EAST WEST UNIVERSITY

Drug designing based on annual survey using SQL

A project Submitted

By

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Abstract

In this research, National health services server in Bangladesh is developed, which is highly useful for us as well all over the world. As a modern civilization requires digitalization, as a result the need of application is increasing everywhere. It not only save our health data but also give annual survey reports. Firstly, an effective registered doctor based digital prescription is designed. This has done through Java script and CSS for making it usable to the all kinds of user. Doctor and patient overviewsare observed on several diseases and developed this web application. Secondly, a server is developed using Server Query Language (SQL), which will be accumulated with national server. As it is already described that it will be national level health database, it is also capable of saving all kind of data from doctor prescription. Therefore, both doctor and patients will be able to retain their previous prescription or overview of any disease. Again, the number of quack doctor will be decreased as admin label has extra securitythat not all users are capable to input data only registered doctor can input the data.

Declaration

I hereby declare that, this project has done under ICE498 and has not submitted elsewhere for requirement of any degree or diploma or for any purpose except for publication.

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Letter of Acceptance

We hereby declare that this project is from the student's own work and best effort of mine, and all other source of information used have been acknowledge. This project has submitted with our approval.

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We cannot forget our sincere honorable faculty of ECE in the academic interactions and company they have accorded to us especially Dr. Md. Moffazol Hossain, Chairperson, Department of ECE, East West University. They will always be remembered as their great contribution, friendly attitude, enthusiastic support and perfect guidance from the beginning to the end.

We are very grateful for the motivation and stimulation from my friends and seniors. Finally, our most heartfelt gratitude goes to our beloved parents, brothers and sisters for their endless support, continuous inspiration.

Chapter 1

1.1 INTRODUCTION:

Bangladesh is a small country with large number of population. We have shortage of 60000 nurse, 2,80,000 nurse and technologist. The people of our country are suffering from malnutrition and many other diseases. Among them, there are some diseases, which suffered much such as, Chikungunya, Diarrhea etc.

1.2 CHIKUNGUNYA:

Chikungunya is an illness caused by a virus that spreads through mosquito bites. The most common symptoms of chikungunya are fever and joint pain. Other symptoms may include headache, muscle pain, joint swelling, or rash.

Chikungunya is an infection caused by the chikungunyavirus (CHIKV).Symptoms include fever and joint pain. These typically occur two to twelve days after exposure. Other symptoms may include headache, muscle pain, joint swelling, and a rash. Most people are better within a week; however, occasionally the joint pain may last for months. The risk of death is around 1 in 1,000. The very young, old, and those with other health problems are at risk of more severe disease.

The virus is spread out between people by two types of mosquitoes: Aides albopictus and Aides. They mainly bite during the day. The virus may circulate within a number of animals including birds and rodents. Diagnosis is by either testing the blood for the virus's RNA or antibodies to the virus. The symptoms can be mistaken for those of dengue fever and Zika fever. After a single infection, it is believed most people become immune.

The best means of prevention is overall mosquito control and the avoidance of bites in areas where the disease is common. This may be partly achieved by decreasing mosquitoes' access to water and with the use of insect repellent and mosquito nets. There is no vaccine and no specific treatment as of 2016. Recommendations include rest, fluids, and medications to help with fever and joint pain.

While the disease typically occurs in Africa and Asia, outbreaks have been reported in Europe and the Americas since the 2000s. In 2014 more than a million suspected cases occurred. In 2014 it was occurring in Florida in the continental United States but as of 2016 there was no further locally acquired cases. The

disease was first identified in 1952 in Tanzania. The term is from the Kimakonde language and means "to become contorted".

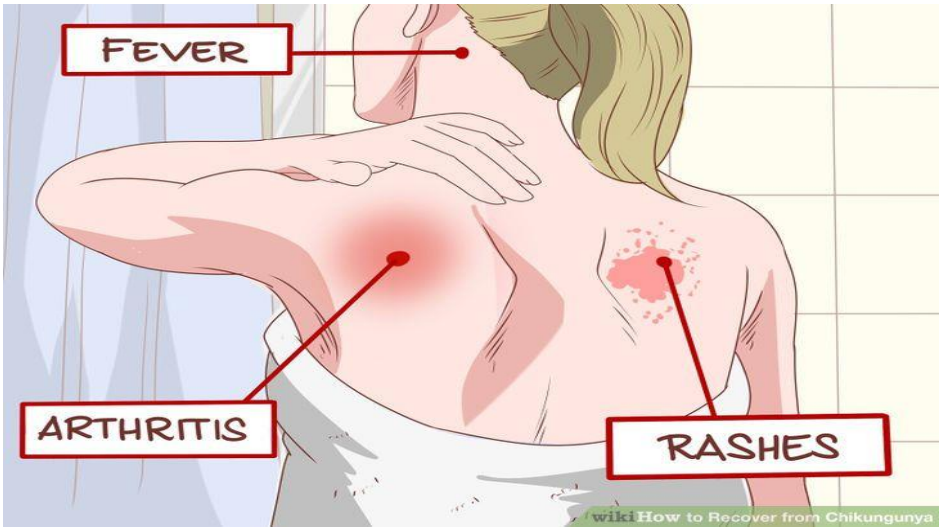

Fig. 1.1: Chikungunya disease

1.3 DIARRHEA:

Diarrhea, also spelled diarrhea, is the condition of having at least three loose or liquid bowel movements each day. It often lasts for a few days and can result in dehydration due to fluid loss. Signs of dehydration often begin with loss of the normal stretchiness of the skin and irritable behavior. This can progress to decreased urination, loss of skin color, a fast heart rate, and a decrease in responsiveness as it becomes more severe. Loose but non-watery stools in babies who are breastfed, however, may be normal.

The most common cause is an infection of the intestines due to either a virus, bacteria, or parasite - a condition also known as gastroenteritis. These infections are often acquired from food or water that has been contaminated by feces, or directly from another person who is infected. The three types of diarrhea are: short duration watery diarrhea, short duration bloody diarrhea, and persistent diarrhea (lasting more than two weeks). The short duration watery diarrhea may be due to an infection by cholera, although this is rare in the developed world. If blood is present it is also known as dysentery. A number of

non-infectious causes can result in diarrhea. These include lactose intolerance, irritable bowel syndrome, non-celiac gluten sensitivity, celiac disease, inflammatory bowel disease, hyperthyroidism, and a number of medications. In most cases, stool cultures to confirm the exact cause are not required.

Diarrhea can be prevented by improved sanitation, clean drinking water, and hand washing with soap. Breastfeeding for at least six months and vaccination against rotavirus is also recommended. Oral rehydration solution (ORS)--clean water with modest amounts of salts and sugar--is the treatment of choice. Zinc tablets are also recommended. These treatments have been estimated to have saved 50 million children in the past 25 years. When people have diarrhea it is recommended that they continue to eat healthy food and babies continue to be breastfed. If commercial ORS are not available, homemade solutions may be used. In those with severe dehydration, intravenous fluids may be required. Most cases; however, can be managed well with fluids by mouth. Antibiotics, while rarely used, may be recommended in a few cases such as those who have bloody diarrhea and a high fever, those with severe diarrhea following travelling, and those who grow specific bacteria or parasites in their stool. Lope amide may help decrease the number of bowel movements but is not recommended in those with severe disease.

About 1.7 to 5 billion cases of diarrhea occur per year. It is most common in developing countries, where young children get diarrhea on average three times a year. Total deaths from diarrhea are estimated at 1.26 million in 2013 – down from 2.58 million in 1990. In 2012, it was the second most common cause of deaths in children younger than five (0.76 million or 11%). Frequent episodes of diarrhea are also a common cause of malnutrition and the most common cause in those younger than five years of age. Other long term problems that can result include stunted growth and poor intellectual development.

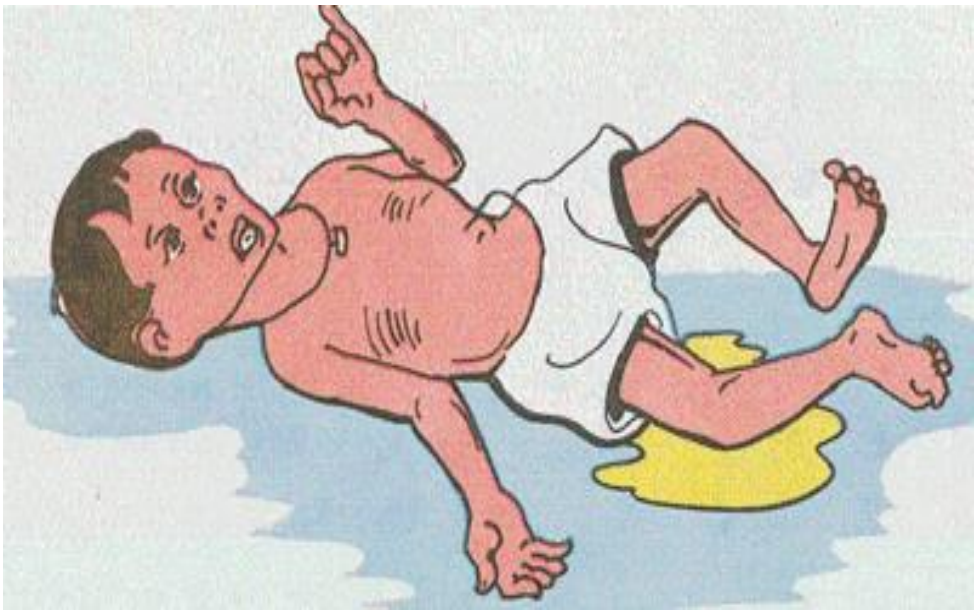

Fig. 1.2: Diarrhea Diseases

1.3 PROBLEM WITH PREVIOUS REPORT:

Suppose after going to any doctor we forget to take our previous report with us. Then what we do after that ? If we can get our all report at a time without carrying them what will happen. Otherwise, the doctor can't understand properly.

Fig. 1.3: Forgetting to take previous report

1.4 QUACK-DOCTOR:

Have you ever faced any death, whichis occurred by wrong treatment? Yes, The country had faced many of this problem previously or recently. After opening the newspaper we see this occurrences regularly. This is happen only because of Quack doctors or well trained doctor.

The population of our country can't accommodate with the number of doctor. And for illiteracy, Lack of public awareness the quack doctors are arise.

Quackery is the promotion of fraudulent or ignorant medical practices. A quack is a "fraudulent or ignorant pretender to medical skill" or "a person who pretends, professionally or publicly, to have skill, knowledge, qualification or credentials he or she does not possess; a charlatan or snake oil salesman". The term quack is a clipped form of the archaic term quacksalver, from Dutch: kwakzalver a "hawker of salve".In the Middle Ages the term quack meant "shouting". The quacksalvers sold their wares on the market shouting in a loud voice.

Common elements of general quackery include questionable diagnoses using questionable diagnostic tests, as well as untested or refuted treatments, especially for serious diseases such as cancer. Quackery is often described as "health fraud" with the salient characteristic of aggressive promotion.

Fig.1.4: Quack doctor

1.5 LITERATURE REVIEW:

- In 2010, Drug designing prescription was proposed in Estonia which was lasted 5 years.
- There may be some European country who are worked on this.
- Dr. Fredric Bjorkling(University of Copenhagen ,Denmark) ,Dr. GjumrakchAliev (University Atlanta ,USA) , Dr. Teodeng (houstanmetholist research institute) worked on digital Prescription.

Fig. 1.5: Who worked on Drug Designing previous (Dr. FREDLIC, Dr.GJUMRAKCH , Dr. TEO ALIEV)

Digital prescriptionis the computer-based electronic generation, transmission and filling of a medical prescription, taking the place of paper and faxed prescriptions. E-prescribing allows a physician, pharmacist, nurse practitioner, or physician assistant to electronically transmit a new prescription or renewal authorization to a community or mail-order pharmacy. It outlines the ability to send error-free, accurate, and understandable prescriptions electronically from the healthcare provider to the pharmacy. E-prescribing is meant to reduce the risks associated with traditional prescription script writing. It is also one of the major reasons for the push for electronic medical records. By sharing medical prescription information, e-prescribing seeks to connect the patient's team of healthcare providers to facilitate knowledgeable decision making.

1.6 PROPOSED METHOD:

By implementing drug designing, we can eradicate Quack doctors. We can get medical assistance of annual survey. We get previous report easily. If government accept our proposal , one day there will be no Quack Doctors..

Drug discovery scientists are all aiming to identify compounds and candidate drugs with 'good' properties that are safe and efficacious, as quickly and cheaply as possible. The standard approach of the last 20 years has been to identify a single molecule disease target, and then to identify a compound that interacts with and modulates this target with high specificity. However, there is now a growing realization that this 'one target – one drug' approach doesn't work well, and that screening huge libraries of compounds against one particular property of an isolated target is an inefficient way to discover potential drugs. Much of the innovation currently seen in drug discovery methodologies seeks to access and integrate more information – about targets, compounds, and disease phenotypes – to enable a more comprehensive and holistic approach to discovering 'good' drug candidates. This article does not try to crystal ball-gaze deep into the future, but rather to identify those trends in the adoption of new technologies and approaches that are gaining traction now, and that can be expected to become more prevalent in the next two to three years.

Research papers do not necessarily reflect the latest trends and thinking in technology adoption, due to the time required for manu – script preparation, submission, review, and publication. I have therefore reviewed infor – mation that has been reported at significant recent scientific conferences in order to identify some of the key technology trends in the field. These conferences included SLAS 2012, ELRIG's Drug Discovery 2012 and the 2012 MipTec conference. I've also examined the programme for the January 2013 SLAS conference, and a next-generation sequencing conference (also in January 2013: Hanson Wade's NGS-Pharma). From these, three technology areas stand out as being both particularly active, and also genuinely useful to drug discovery scientists.

These are:

- increasing the throughput of key, but relatively slow, technologies
- wider adoption of label-free techniques, and the introduction of new ones
- better model systems for screening assays.

In addition to these three areas, there are two other striking features that emerge from these recent conferences. One is that difficult target areas are receiving more attention from researchers, and this is driving innovation in technology. The second is the growing realisa – tion that prior knowledge of specific molecular targets is not only unnecessary, but may actually hamper discovery efforts. Phenotypic drug discovery (PDD) is becoming more widely used (partly driven by the improved model systems and the means to interrogate them) and has been shown to be an efficient method for discovering 'first-in-class' drugs[2].

Mass spectrometry (MS) has been routinely used to assay the metabolism of compounds in lead optimisation and preclinical development for 20 or so years; fewer drugs now fail as a result of pharmacokinetic issues thanks to MS. The increasing size of chemical libraries, highthroughput screening (HTS) technologies that enable thousands or millions of compounds to be screened, and the concomitant increase in compounds requiring optimisation over this period have increased the urgency for the bioanalysis of metabolites, and a need for faster turnaround. In addition to new analytical techniques for MS that give more sensitivity and require less sample preparation, there has also been a drive to increase the throughput of MS. As examples, Agilent's RapidFirehighthroughput MS system has been used both to read a cytochrome P450 inhibition assay at Bristol-Myers Squibb (A Weston, SLAS 2013), using human liver microsomes, and also to detect inhibitors of histone demethylases in human macrophages at GSK[3] (M Leveridge, Drug Discovery 2012). RapidFire requires no offline sample preparation, and permits sample times of 6 to 10 seconds. San Diego-based NextVal (www.nextval.com) has introduced a high-throughput MS system that generates spectra from acoustically printed arrays with a matrix-free direct surface

ionisation technology – this avoids significant barriers associated with the use of matrix-based ionisation methods in screening. NextVal's technology is currently being evaluated by Bristol-Myers Squibb.

Flow cytometry is a well-established cellular analysis technique whose value has been demonstrated in clinical laboratories all over the world. One of the most useful attributes of flow cytometry is its ability to collect multiparametric molecular and functional data from individual cells – it is a very high-content technique. Imaging high-content screening (HCS) has already proven its worth in compound screening and drug discovery, but the throughput issues of flow cytometry have limited its impact. Advances in flow cytometry instrumentation, such as Beckman's MoFlo instrumentation and Amnis' imaging flow cytometers, have now increased the throughput and information content available. Highthroughput flow cytometers are beginning to become useful tools in compound screening, and have been used by GSK for cell-based screening of histone demethylase inhibitors (R Jepras, SLAS 2013, HyperCyt high-through sampler and Accuri cytometer) and for a screening assay in haematopoietic target identification at the Czech Institute of Molecular Genetics (P Bartumek, SLAS 2013). However, Purdue University's cytometry guru, Paul Robinson, believes that the availability of appropriate analytical tools to process and interrogate high-throughput flow cytometry data is becoming a rate-limiting step in the widespread adoption of high-throughput flow cytometry (SLAS 2013). However, highthroughput flow cytometry does have the power to establish functional relationships between cellular phenotypes, key activator molecules and their modulation states, and compound activity all within single cells, and it is now being applied to drug screening.

Chapter 2

DRUG DESIGNING

- Drug Designing
- Rational Drug Designing
- Computer Aided Drug Designing
- Case Studies
- Drug designing journals
- Screening and Drug Designing
- Aims and Scope.

2.1 DRUG DESIGNING:

Drug Design,often referred to as **rational drug design** or simply **rational design**, is the inventive process of finding new medications based on the knowledge of a biological target.The drug is most commonly an organics mall that activates or inhibits the function of a bimolecular such as a protein, which in turn results in a therapeutic benefit to the patient [1]. In the most basic sense, drug design involves the design of molecules that are complementary in shape and charge to the bio-molecular target with which they interact and therefore will bind to it. Drug design frequently but not necessarily relies on computer modeling techniques.This type of modeling is sometimes referred to as **computer-aided drug design**. Finally, drug design that relies on the knowledge of the three-dimensional structure of the bimolecular target is known as **structure-based drug design**. In addition to small molecules, biopharmaceuticals and especially therapeutic antibodies are an increasingly important class of drugs and computational methods for improving the affinity, selectivity, and stability of these protein-based therapeutics have also been developed.[1]The phrase "drug design" is to some extent a misnomer. A more accurate term is ligand design (i.e., design of a molecule that will bind tightly to its target). Although design techniques for prediction of binding affinity are reasonably successful, there are many other properties, such as bioavailability, metabolic half-life, side effects, etc., that first must be optimized before a ligand can become a safe and efficacious drug [1]. These other characteristics are often difficult to predict with rational design techniques. Nevertheless, due to high attrition rates, especially during clinical phases of drug development, more attention is being focused early in the drug design process on selecting candidate drugs whose physicochemical properties are predicted to result in fewer complications during development and hence more likely to lead to an approved,

marketed drug. Furthermore, in vitro experiments complemented with computation methods are increasingly used in early drug discovery to select compounds with more favorable ADME (absorption, distribution, metabolism, and excretion) and toxicological profiles [1].

A bimolecular target (most commonly a protein or nucleic acid) is a key molecule involved in a particular metabolic or signaling pathway that is associated with a specific disease condition or pathology or to the infectivity or survival of a microbial pathogen. Potential drug targets are not necessarily disease causing but must by definition be disease modifying. In some cases, small molecules will be designed to enhance or inhibit the target function in the specific disease modifying pathway. Small molecules (for example receptor agonists, antagonists, inverse agonists, or modulators; enzyme activators or inhibitors; or ion channel openers or blockers)will be designed that are complementary to the binding site of target [2]. Small molecules (drugs) can be designed so as not to affect any other important "off-target" molecules (often referred to as antitragi's) since drug interactions with off-target molecules may lead to undesirable side effects. Due to similarities in binding sites, closely related targets identified through sequence homology have the highest chance of cross reactivity and hence highest side effect potential [2].

Most commonly, drugs are organics mall produced through chemical synthesis, but biopolymer-based drugs (also known as biopharmaceuticals) produced through biological processes are becoming increasingly more common. In addition, mRNA-based gene silencing technologies may have therapeutic applications [2].

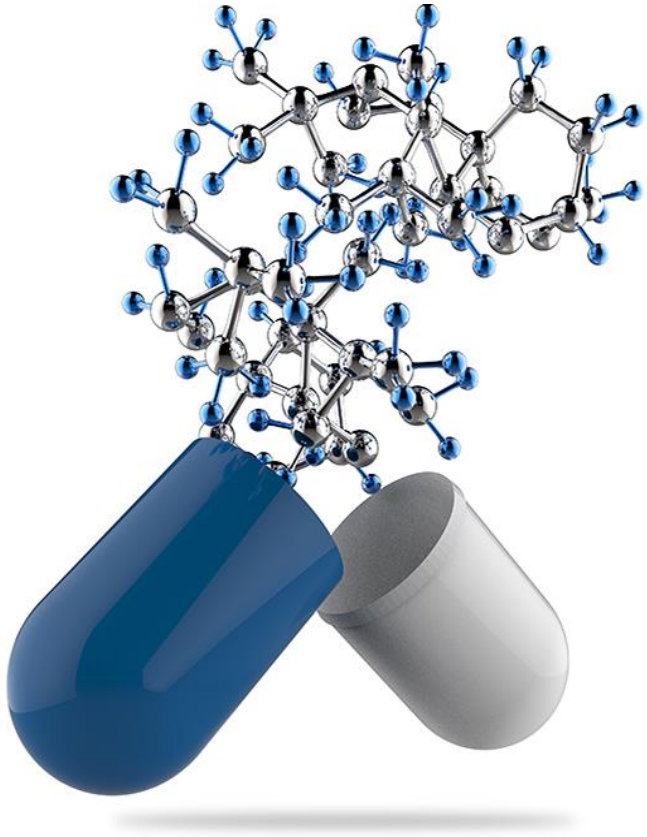

Fig. 2.1: **drug**

2.2 Rational drug discovery :

In contrast to traditional methods of drug discovery (known as forward pharmacology), which rely on trial-and-error testing of chemical substances on cultured cells or animals, and matching the apparent effects to treatments, rational drug design (also called reverse pharmacology) begins with a hypothesis that modulation of a specific biological target may have therapeutic value [4]. In order for a bimolecular to be selected as a drug target, two essential pieces of

information are required [3]. The first is evidence that modulation of the target will be disease modifying. This knowledge may come from, for example, disease linkage studies that show an association between mutations in the biological target and certain disease states. The second is that the target is "drug gable". This means that it is capable of binding to a small molecule and that its activity can be modulated by the small molecule[5].

Once a suitable target has been identified, the target is normally cloned and produced and purified. The purified protein is then used to establish a screening assay. In addition, the three-dimensional structure of the target may be determined [6].

The search for small molecules that bind to the target is begun by screening libraries of potential drug compounds. This may be done by using the screening assay (a "wet screen")[8]. In addition, if the structure of the target is available, a virtual screenmay be performed of candidate drugs. Ideally the candidate drug compounds should be "drug-like", that is they should possess properties that are predicted to lead to oral bioavailability, adequate chemical and metabolic stability, and minimal toxic effects. Several methods are available to estimate drug likeness such as Lipinski's Rule of Five and a range of scoring methods such as lipophilic efficiency.Several methods for predicting drug metabolism have also been proposed in the scientific literature [9].

Due to the large number of drug properties that must be simultaneously optimized during the design process, multi-objective optimization techniques are sometimes employed.Finally because of the limitations in the current methods for prediction of activity, drug design is still very much reliant on serendipity and bounded rationality.

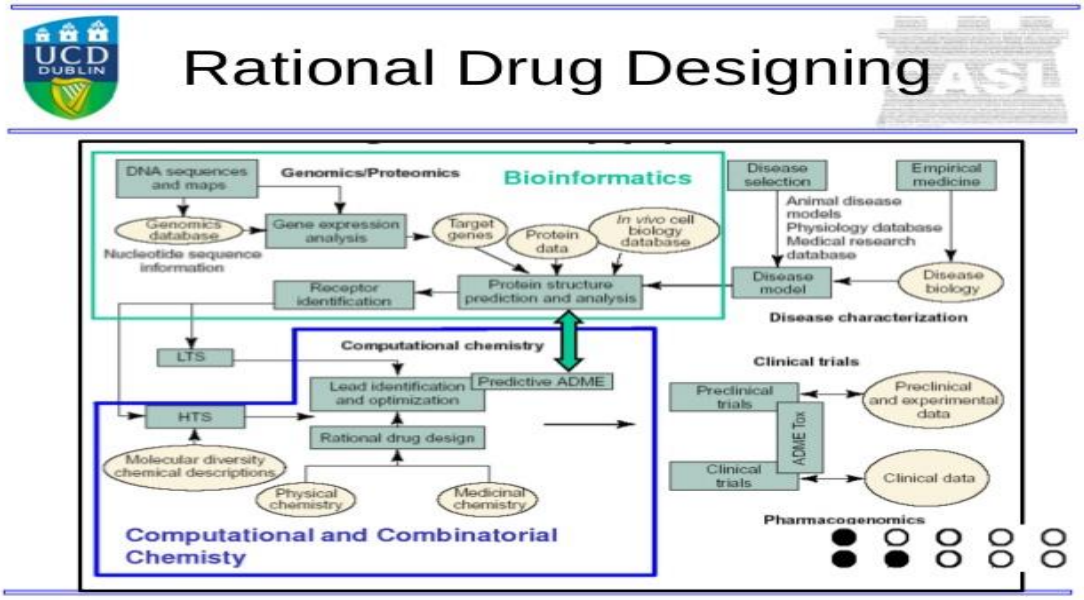

Fig.2.2: Rational Drug Designing

2.3 Computer-aided Drug Design :

The most fundamental goal in drug design is to predict whether a given molecule will bind to a target and if so how strongly. Molecular mechanics or molecular dynamicsis most often used to estimate the strength of the intermolecular interaction between the small molecule and its biological target. These methods are also used to predict the conformation of the small molecule and to model conformational changes in the target that may occur when the small molecule binds to it. Semi-empirical, an initio quantum chemistry methods, or density functional theory are often used to provide optimized parameters for the molecular mechanics calculations and also provide an estimate of the electronic properties (electrostatic potential, polarizability etc.) of the drug candidate that will influence binding affinity[10].

Molecular mechanics methods may also be used to provide semi-quantitative prediction of the binding affinity. Also, knowledge-based scoring function may be used to provide binding affinity estimates. These methods use linear regression, machine learning, neural nets or other statistical techniques to derive predictive binding affinity equations by fitting experimental affinities to computationally derived interaction energies between the small molecule and the target[9].

Ideally, the computational method will be able to predict affinity before a compound is synthesized and hence in theory only one compound needs to be synthesized, saving enormous time and cost. The reality is that present computational methods are imperfect and provide, at best, only qualitatively accurate estimates of affinity. In practice it still takes several iterations of design, synthesis, and testing before an optimal drug is discovered. Computational methods have accelerated discovery by reducing the number of iterations required and have often provided novel structures[11-17].

Drug design with the help of computers may be used at any of the following stages of drug discovery:

1. hit identification using virtual screening (structure- or legend-based design)
2. hit-to-lead optimization of affinity and selectivity (structure-based design, QSAR, etc.)
3. lead optimization of other pharmaceutical properties while maintaining affinity

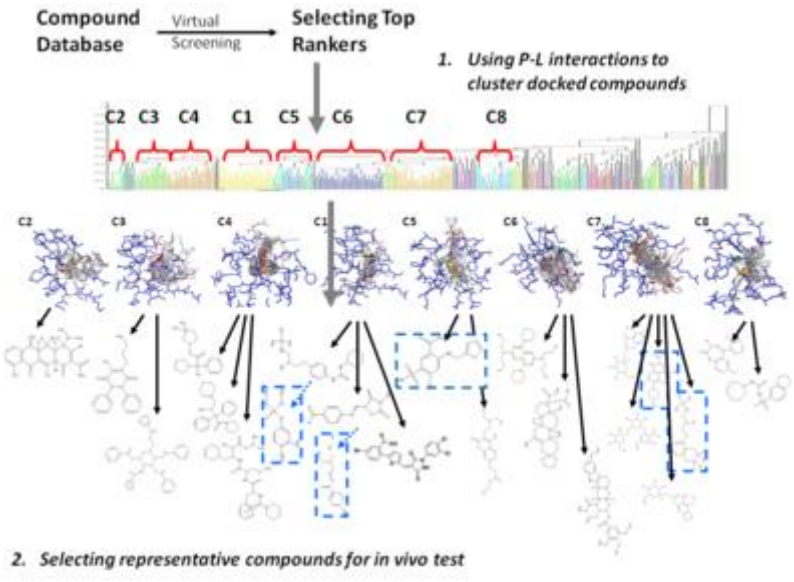

Fig .2.3

Flowchart of a Usual Clustering Analysis for Structure-Based Drug Design

In order to overcome the insufficient prediction of binding affinity calculated by recent scoring functions, the protein-ligand interaction and compound 3D structure information are used for analysis. For structure-based drug design, several post-screening analyses focusing on protein-ligand interaction have been developed for improving enrichment and effectively mining potential candidates:

- Consensus scoring
    - Selecting candidates by voting of multiple scoring functions
    - May lose the relationship between protein-ligand structural information and scoring criterion

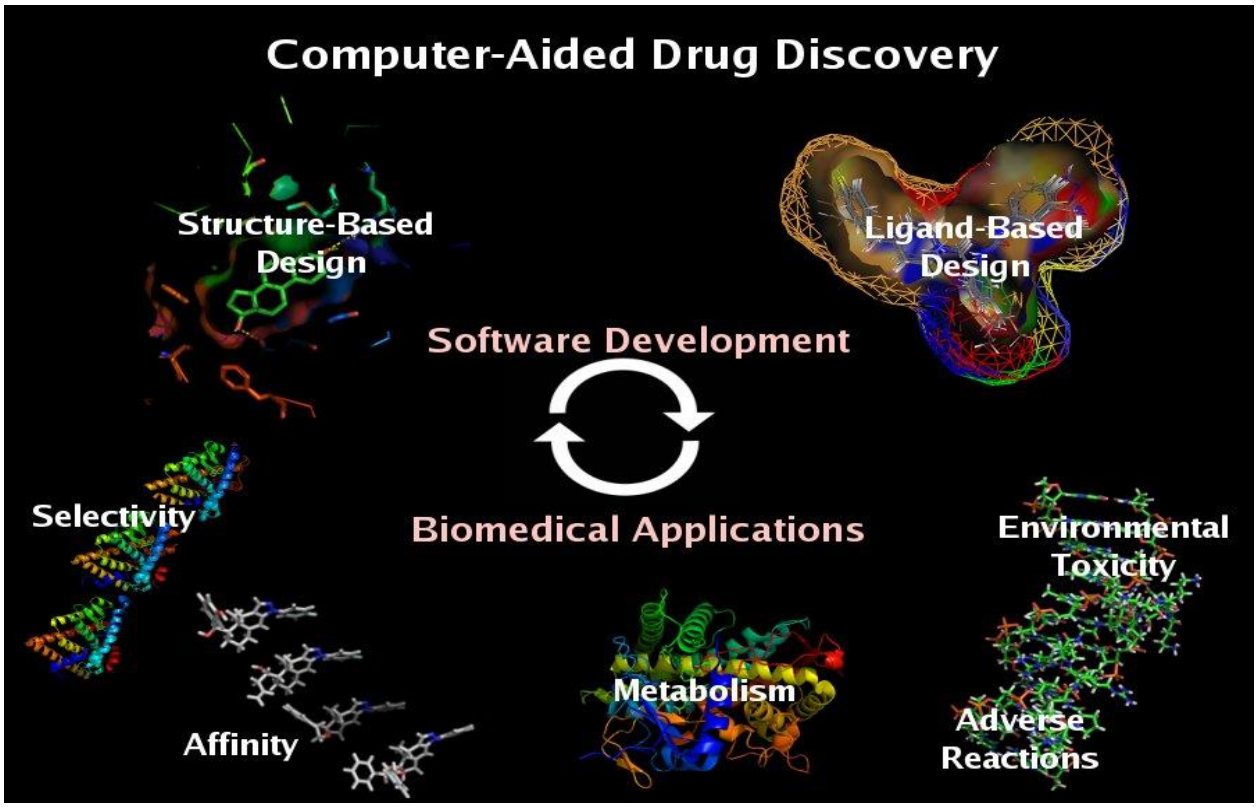

Fig 2.4: Computer Aided Drug designing

- **Cluster Analysis :**
    - Represent and cluster candidates according to protein-ligand 3D information
    - Needs meaningful representation of protein-ligand interactions.

Legend-based drug design (or **indirect drug design**) relies on knowledge of other molecules that bind to the biological target of interest. These other molecules may be used to derive a pharmacophore model that defines the minimum necessary structural characteristics a molecule must possess in order to bind to the target[21]. In other words, a model of the biological target may be built based on the

knowledge of what binds to it, and this model in turn may be used to design new molecular entities that interact with the target. Alternatively, a quantitative structure-activity relationship (QSAR), in which a correlation between calculated properties of molecules and their experimentally determined biological activity, may be derived. These QSAR relationships in turn may be used to predict the activity of new analogs[20].

Structure-based :

Structure-based drug design (**Direct Drug Design**) relies on knowledge of the three dimensional structure of the biological target obtained through methods such as x-ray crystallography or NMR spectroscopy.If an experimental structure of a target is not available, it may be possible to create a homology model of the target based on the experimental structure of a related protein. Using the structure of the biological target, candidate drugs that are predicted to bind with high affinity and selectivity to the target may be designed using interactive graphics and the intuition of a medicinal chemist. Alternatively various automated computational procedures may be used to suggest new drug candidates[3].

Current methods for structure-based drug design can be divided roughly into three main categories.The first method is identification of new legends for a given receptor by searching large databases of 3D structures of small molecules to find those fitting the binding pocket of the receptor using fast approximate docking programs. This method is known as virtual screening.[4] A second category is de novo design of new legends. In this method, legend molecules are built up within the constraints of the binding pocket by assembling small pieces in a stepwise manner. These pieces can be either individual atoms or molecular fragments. The key advantage of such a method is that novel structures, not contained in any

database, can be suggested.A third method is the optimization of known legends by evaluating proposed analogs within the binding cavity[5].

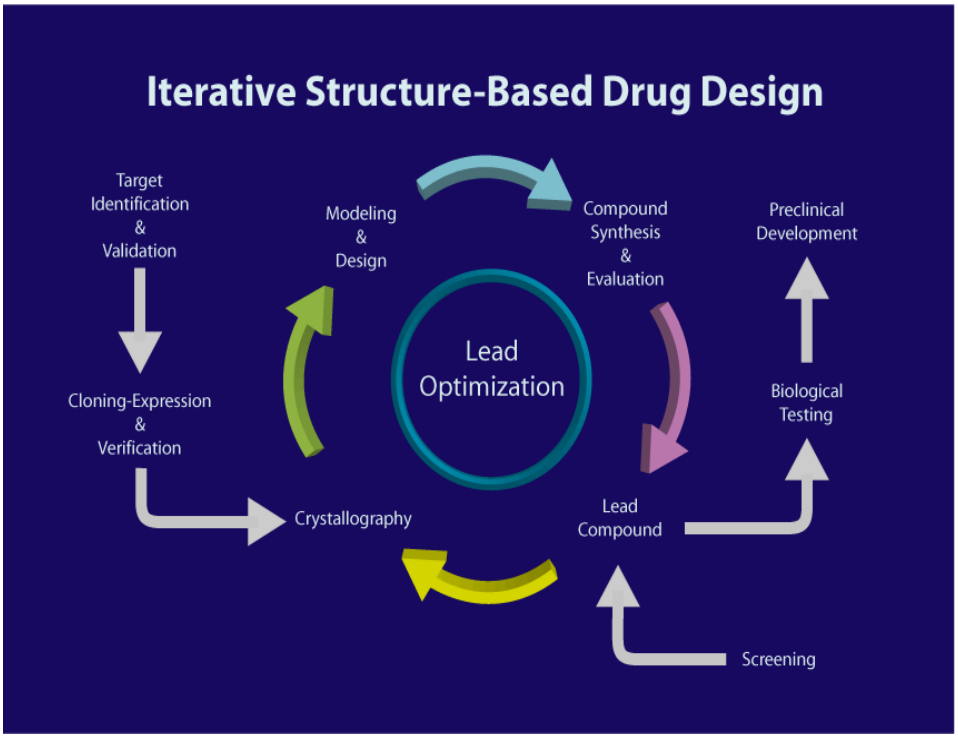

Fig.2.5:Iterative Structure

2.4 Binding site Identification:

Binding site identification is the first step in structure based design. If the structure of the target or a sufficiently similar homolog is determined in the presence of a bound legend, then the legend should be observable in the structure in which case location of the binding site is trivial. However, there may be unoccupied allosteric binding sites that may be of interest. Furthermore, it may be that only apoprotein (protein without legend) structures are available and the reliable identification of unoccupied sites that have the potential to bind legends with high affinity is non-trivial. In brief, binding site identification usually relies on identification of concave surfaces on the protein that can accommodate drug sized molecules that

also possess appropriate "hot spots" (hydrophobic surfaces, hydrogen bonding sites, etc.) that drive legend binding[7].

Structure-based drug design attempts to use the structure of proteins as a basis for designing new legends by applying the principles of molecular recognition. Selective high affinity binding to the target is generally desirable since it leads to more efficacious drugs with fewer side effects. Thus, one of the most important principles for designing or obtaining potential new legends is to predict the binding affinity of a certain legend to its target (and known antitragi's) and use the predicted affinity as a criterion for selection[21].

One early general-purposed empirical scoring function to describe the binding energy of legends to receptors was developed by Böhm. This empirical scoring function took the form:

2.5 Case Studies

- 5-HT3 antagonists
- Acetylcholine receptor agonists
- Angiotensin receptor antagonists
- Bcr-Abl tyrosine- kinas inhibitors
- Cannabinoid receptor antagonists
- CCR5 receptor antagonists
- Cyclooxygenase 2 inhibitors
- Dipeptidyl peptidase-4 inhibitors
- HIV protease inhibitors
- NK1 receptor antagonists

- Non-nucleoside reverse transcriptase inhibitors
- Nucleoside and nucleotide reverse transcriptase inhibitors
- PDE5 inhibitors
- Proton pump inibitors
- Renin inhibitors
- Triptans
- TRPV1 antagonists
- c-Met inhibitors

2.6 Drug Designing journal :

The Journal, Drug Designing Open Access publishes the highest quality scientific articles amalgamating broad range of fields including molecular modeling, clinical research and drug discovery and delivery.

The journal focuses on all fields of drug design including drugdiscovery, drug design by rational approach, target-based design, drug synthesis, drug metabolism, structure-based drug design, molecular modeling, ligand-based interaction, development of the generic drug, in siliconchemoinformatics and bioinformatics technologies, receptor agonist/antagonist, protease substrate/inhibitor, peptidomimetic, Quality by design, Design for reliability in drug development, Design for traditional Chinese medicine clinical trials, Bayesian sequential design for multi-regional design, Design and analysis for target clinical trials, Design and analysis for diagnostic procedures, Adaptive design for early clinical development, Design for biosimilar studies, Design for bioassay development and validation,

Design for statistical genetics, Design for assessment of drug to drug interaction, Design for bridging studies, Design for stability analysis, etc [30-39].

This scientific journal includes a wide range of fields in its discipline to create a platform for the authors to make their contribution towards the journal and the editorial office at Omics International promises a peer review process for the submitted manuscripts to maintain the quality of free journals. The journal is among the best open access journals and aims to publish most complete and reliable source of information on the discoveries and current developments in the mode of original articles, review articles, case reports, short communications, etc. in all areas of the field[26].

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Drug designing journals have been showing tremendous citations and articles focusing the most advanced research trends in the field of drug discovery, medicinal chemistry, Drug Design tools, protein engineering, bioinformatics. Editorial Manager is an online manuscript submission, review and tracking systems. Review processing is performed by the editorial board members of Drug Designing: Open Access or outside experts; at least two independent reviewer's approval followed by editor approval is required for acceptance of any citable manuscript. Authors may submit manuscripts and track their progress through the system, hopefully to publication. Reviewers can download manuscripts and submit their opinions to the editor. Editors can manage the whole submission/review/revise/publish process[29].

3.7 Drug Designing Based on Journals

Drug design is an splendid inventive process of new medication on the basis of biological target. It is also known as rational drug design or rational design. That is the invention in medical history in order to yield significant therapeutic response. The drug is an organic molecule, when it is bind to target site it can either inhibit or activate the function of a bimolecular which results in therapeutic benefit. The drug design involves the design of such molecules that are similar to the bio molecular target site in shape and charge in order to bind to it. Drug design relies on the knowledge of the three dimensional structure of bimolecular targets[35].

2.8 Related Journals of Drug Designing

International Journal of Drug Development & Research, Pharmaceutics & Drug Delivery Research, Chemical Biology and Drug Design, Anti-Cancer Drug Design, Drug Design, Development and Therapy, Drug Design and Discovery, Current Computer-Aided Drug Design, Advances in Antiviral Drug Design, Drug Design Reviews Online, Frontiers in Drug Design and Discovery and International Journal of Computational Biology and Drug Design[19].

2.8.1 Fragment Based Drug Design:

Fragment based drug design is identification of fragments or components of low molecular weight or lead compounds, which can bind with weak affinity to the target site. Fragment based discovery involved finding such weakly binding fragments and grow them or combine them in order to create lead components with higher affinity or selectivity to bimolecular target site. These techniques achieved credible success in drug development[23].

2.8.2 Structure Based Drug Design :

Structure based drug design is the process of designing a chemical structure with the objective of identifying a compound which suits for clinical tests. The process involves how that shapes and charges to interact with biological targetinorder to yield therapeutic activity. Structure based drug design based on three-dimensional structures strictly[31].

2.9 Molecular Modeling

Molecular modeling is a tool, which help in the generation, manipulation or representation of three-dimensional structures of molecule and associated physico chemical properties as well. It involves use of computerized techniques based on theoretical chemistry methods and experimental data to predict molecular and biological properties. Molecular modeling help to investigate, interpret and discovery of new phenomena [37].

2.10 Heat Shock Proteins:

Heat shock proteins are the proteins that produced when cells are exposing to the biologically stressful conditions. Some selected heat shock proteins also known as chaperones. Increased temperature and some internal changes such as P^H change will lead to the proteins to denature which cannot morphologically, functionally normal and leads to unfold of proteins that miss folded proteins aggregates and eventually kills the cell. Heat Shock Proteins are induced rapidly at high levels to deal with this problem. These can able to mediate the synthesis, stability andtranslation ability of mRNA[36].

2.11ANTIGEN-ANTIBODY:

Antigen – antibody reaction is a chemical interaction between antigens of cell surface and antibodies which are produced by the B-lymphocytes of the white blood cells. Each antibody can bound with specific antigen which is due to specific chemical constitution of the particular antibody. I it doesn't happen so it leads to cross linking which is fatal . This is the reaction which keeps the body free from and protected from pathogens, chemical toxins and foreign bodies. Immunity of the humans is mediated by this specific phenomena[21].

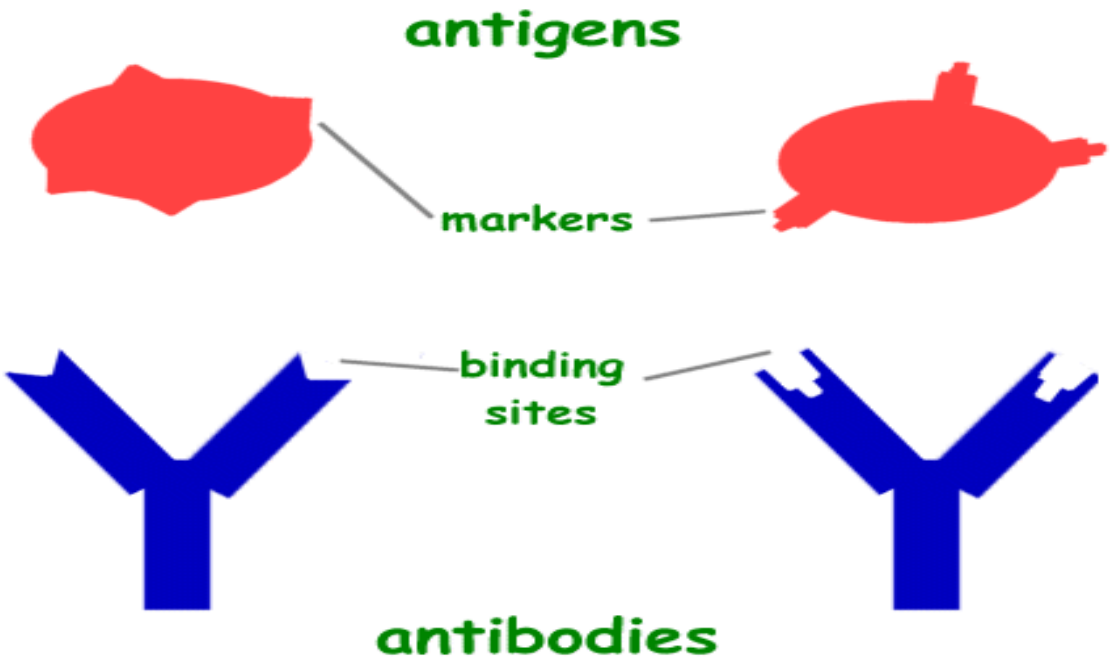

Fig.2.6: Antigens

Nano medicals:

Nano medicine is the application of the nanotechnology, which ranges from application of nanomaterials to nanoelectronicbiosensors medicinally. The functionality can be attain to nanomedicine by interact with them biomolecule. As most of nanomaterial structure is similar to the biological structures these can be widely useful for in vitro and in vivo researches. With of invention its widely using in the development of diagnostic devices, analytical tools, drug delivery vehicles and physical therapy applications[40].

Receptor Agonist/ Antagonist

In pharmacology the agonist- antagonist are the type of receptor ligand or drug which binds to the receptor and mediates the therapeutic response either by activates or blocks the receptor.Agonists activates receptors to produce desired action whereas the antagonists blocks the action of agonist upon the binding to receptor. inverse agonist causes to action against to that of agonist[33].

Peptidomimetic

Peptidomimetics are the compounds whose pharmacophores that is their essential elements mimic a natural peptide or protein in order to retain the ability to interact with the specified biological target and produce same biological effect. This can form either rom modification of the persistent peptide or by designing the peptoids and β-peptides. With the changed structure can attain significant molecular properties like desired biological activity and stability[32].

Protease Substrate/Inhibitor

Proteases are the enzymes that are responsible for proteolysis that is cleave of proteins by hydrolysis of peptide bonds that links amino acids which are in peptide chain. These are responsible for many life and death processes. Whereas protease inhibitors are blocks the activity of protease enzymes which helps in the growth life threatening viruses and immature them and make them unable to infect new cells.

Screening and Drug Design

Virtual screening is a computational method which plays a key role in drug discovery. it is used to search small molecule libraries to find the structures those which likely bind or interact with drug target. It is also defined as "automatically evaluating very large libraries of compounds" using computer programs. As the accuracy of this method is increased it is widely using in drug designprocess[31].

2.12 Drug Delivery using Nanotechnology

Nanotechnology includes the engineering of functional systems at the molecular scale which are characterized by unique physical, optical and electronic features that are attractive for disciplines ranging from materials science to biomedicine. The use of nanotechnology in drug development is the developing process where the nanoparticles used to deliver the drug to the particular cell which is diseased. By this technology the particles which are engineered in such a way that they can attract to the diseased cell and allows treatment to the particular cell directly. Through this unique technique can minimize the damage of healthy cells in the body.

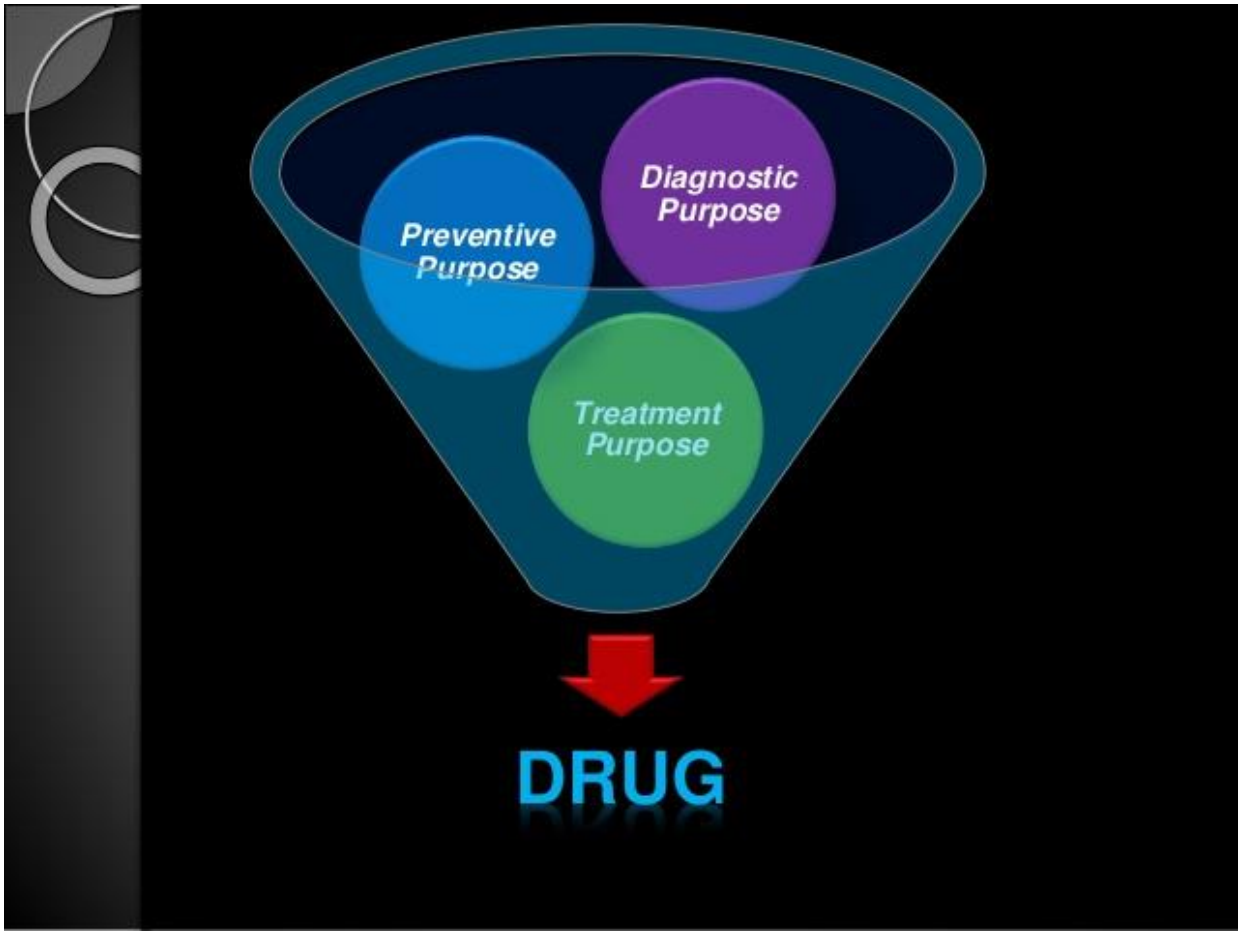

Fig.2.7:Drug Delivery using Nanotechnology

2.13Aims and Scope

- The Journal, Drug Designing Open Access publishes the highest quality scientific articles amalgamating broad range of fields including molecular modeling, clinical research, and drug discovery and design. The journal focuses on all fields of drug design including drug discovery, drug design by rational approach, target-based design, drug synthesis, drug metabolism, Structure-based drug design, molecular modeling, ligand-based interaction, Development of the generic drug, in silicochemoinformatics and bioinformatics technologies, Receptor agonist/antagonist, protease substrate/inhibitor, peptidomimetic.

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- A complete version of the work and all supplemental materials, including a copy of the permission as stated above, in a suitable standard electronic format is deposited immediately upon initial publication in at least one online repository that is supported by an academic institution, scholarly society, government agency, or other well-established organization that seeks to enable Open Access, unrestricted distribution, interoperability, and long-term archiving (for the biomedical sciences, PubMed Central is such a repository)[29].

STRUCTURE BASED DRUG DESIGNING :

1. 1. STRUCTURE BASED DRUG DESIGN PRESENTED BY ADAM SHAHUL HAMEED REG NO:2014419001 M.TECH-COMPUTATIONAL BIOLOGY DOCKING AND DE NOVO DRUG DESIGN 1
2. 2. INTRODUCTION TO DRUG AND DRUG DESIGN The drug is most commonly an organic small′ molecule that activates or inhibits the function of a bio molecule such as a protein, which in turn results in a therapeutic benefit to the patient. Drug design, or rational drug design or simply′ rational design, is the inventive process of finding new medications based on the knowledge of a biological target. Drug design involves the design of small′ molecules that are complementary in shape and charge to the bio molecular target with which they interact and therefore will bind to it. 2
3. 3. INTRODUCTION TO DRUG AND DRUG DESIGN Drug design frequently but not necessarily relies′ on computer modeling techniques. This type of modeling is often referred to as′ computer aided drug design. Finally, drug design that relies on the knowledge′ of the three-dimensional structure of the bio molecular target is known as structure-based drug design. The phrase “drug design” is to some extent a′ misnomer. A more accurate term is ligand design (i.e.,′ design of a small molecule that will bind tightly to its target). 3
4. 4. BACKGROUND Biomolecular target (proteins or nucleic acids) is a key molecule′ involved in a particular metabolic or signaling pathway that is leading to a specific disease condition or pathology or to the infectivity or survival of a microbial pathogen. In Some cases, small molecules will be

designed to inhibit the target′ function in the specific pathway (diseased state). Small molecules (inhibitors or modulators) will be designed that are′ complementary to the active site/allosteric site of target. In some other cases, small molecules will be designed or developed′ to enhance the normal pathway by promoting specific biomolecular molecules in the normal pathways that may have been affected in the diseased state. 4

5. 5. BACKGROUND Small molecules (drugs) can be designed so as not to affect any other′ important "off-target" molecules or anti targets, since drug interactions with off-target molecules may lead to undesirable side effects. Sequence homology is often used to identify such risks.′ Most commonly, drugs are organic small molecules produced through′ chemical synthesis, but biopolymer-based drugs (also known as biologics) produced through biological processes are becoming increasingly more common. 5
6. 6. INTRODUCTION TO SBDD Structure-based drug design (or direct drug design) relies on′ knowledge of the three dimensional structure of the biological target obtained through methods such as x-ray crystallography or NMR spectroscopy. If an experimental structure of a target is not available, it may be′ possible to create a homology model of the target based on the experimental structure of a related protein. Using the structure of the biological target, candidate drugs that are′ predicted to bind with high affinity and selectivity to the target may be designed using interactive graphics and the intuition of a medicinal chemist. 6
7. 7. X-ray Crystallography NMR Spectroscopy Homology Modeling 7
8. 8. INTRODUCTION TO SBDD Structure-based design is one of the first techniques to be used in′ drug design. Structure based drug design that has helped in the discovery process′ of new drugs. In parallel, information about

the structural dynamics and electronic′ properties about legendsare obtained from calculations. This has encouraged the rapid development of the structure based′ drug design. structure-based drug design can be divided roughly into two′ categories. 1. Ligand based Drug Design Or Database Searching 2. Receptor based Drug Design 8

9. 9. LIGAND BASED DRUG DESIGN The first category is about “finding” ligands for a given receptor, which′ is usually referred as database searching. In this case, a large number of potential ligand molecules are′ screened to find those fitting the binding pocket of the receptor. This method is usually referred as ligand-based drug design.′ The key advantage of database searching is that it saves synthetic′ effort to obtain new lead compounds. 9
10. 10. RECEPTOR BASED DRUG DESIGN Another category of structure-based drug design methods is′ about “building” ligands, which is usually referred as receptor- based drug design. In this case, ligand molecules are built up within the constraints′ of the binding pocket by assembling small pieces in a stepwise manner. These pieces can be either individual atoms or molecular′ fragments. The key advantage of such a method is that novel structures,′ not contained in any database, can be suggested. 10
11. 12. Structure-based Drug Design (SBDD) Molecular Biology & Protein Chemistry 3D Structure Determination of Target and Target-Ligand Complex Modeling Structure Analysis and Compound Design Biological Testing Synthesis of New Compounds If promising Pre-Clinical Studies Drug Design Cycle Natural ligand / Screening 12
12. 13. 13 Ligand database Target Protein Molecular docking Ligand docked into protein’s active site Structure-based Drug Design (SBDD) Pharmacokinetic and Pharmacodynamic optimization

13.14. DOCKING • Docking refers to the ability to position a ligand in the active or a designated site of a protein and calculate the specific binding affinities. • Docking algorithms can be used to find ligands and binding conformations at a receptor site close to experimentally determined structures. • Docking algorithms are also used to identify multiple proteins to which a small molecule can bind. • Some of the docking programs are GOLD (Genetic Optimization for Ligand Docking), AUTODOCK, LUDI, HEX etc. 14

14.15. What is Docking? •Docking attempts to find the "best" matching between two molecules •It includes finding the Right Key for the Lock •Given two biological molecules determine: - Whether the two molecules "interact" - If so, what is the orientation that maximizes the "interaction" while minimizing the total "energy" of the complex Goal: To be able to search a database of molecular structures and retrieve all molecules that can interact with the query structure 15

15.16. Docking Protocol 16

16.17. Generate molecular surface of protein Cavities in the receptor are used to define spheres (blue); the centers are potential locations for ligand atoms. Sphere centersare matched to ligand atoms, to determine possible orientations for the ligand. 104 orientations generated How DOCK works……. 17

17.18. Virtual screening, to identify potential lead compounds from a large dataset Known structures of organic compounds′ Libraries of Virtual Compounds′ Programs calculate affinity for protein′ Narrow down to small number of′possibilities Surface representation that efficiently′ represents the docking surface and identifies the regions of interest (cavities and

protrusions) Surface matching that matches surfaces′ to optimize a binding score 18

18.19. Pose prediction • If we know exactly where and how a known ligand binds... – We can see which parts are important for binding – We can suggest changes to improve affinity – Avoid changes that will ‘clash’ with the protein 19

19.20. • Monte Carlo methods (MC) • Molecular Dynamics (MD) • Simulated Annealing (SA) • Genetic Algorithms (GA) Available in packages: Auto Dock (MC,GA,SA)¬ GOLD (GA)¬Sybyl (MD)¬¬ Introducing flexibility: Whole molecule docking programs Glide (Schrodinger)¬ 20

20.21. MOLECULAR DOCKING Aim:′ To achieve an optimized conformation for both receptor and ligand & the relative orientation between protein and ligand such that the free energy of the overall system is minimized Successful docking methods search high-dimensional spaces effectively and use a′ scoring function that correctly ranks candidate dockings. 21

21.22. IMPORTANCE Molecular Docking Prediction of the binding affinity (Scoring Function) Identification of the ligand’s correct binding geometry (pose) in the binding site (Binding Mode) Rational Design Of Drugs 22

22.23. TYPES OF DOCKING Rigid Docking (Lock and Key) In rigid docking, the internal geometry of both the receptor and ligand are treated as rigid. Flexible Docking (Induced fit) An enumeration on the rotations of one of the molecules (usually smaller one) is performed. Every rotation the energy is calculated; later the most optimum pose is selected. 23

23.24. DOCKING CAN BE BETWEEN…. Protein - Ligand′ Protein – Protein′ Protein – Nucleotide′ 24

24.25. LIGAND – PROTEIN DOCKING 25

25.26. LIGAND-PROTEIN DOCKING 26

26.27. TYPES OF INTERACTIONS Electrostatic forces - Forces with electrostatic origin are due to the charges residing in′ the matter. Electrodynamics forces - The most widely known is probably the van der Waals′ interaction. Steric forces - These are caused by entropy. For example, in cases where entropy is′ limited, there may be forces to minimize the free energy of the system. Solvent-related forces – These are due to the structural changes of the solvent. These′ structural changes are generated, when ions, colloids, proteins etc, are added into the structure of solvent. The most commonly are Hydrogen bond and hydrophobic interactions 27

27.28. A TYPICAL DOCKING WORKFLOW TARGET SELECTION LIGAND SELECTION TARGET PREPARATION EVALUATING DOCKING RESULT DOCKING LIGAND PREPARATION 28

28.29. Receptor selection and preparation Building the Receptor The 3D structure of the receptor should be considered which can be downloaded from PDB. The available structure should be processed. The receptor should be biologically active and stable. Identification of the Active Site The active site within the receptor should be identified. The receptor may have many active sites but the one of the interest should be selected. Ligand selection and preparation Ligands can be obtained from various databases like ZINC, PubChem or can be sketched using tools like Chemsketch. Docking The ligand is docked onto the receptor and the interactions are checked. The scoring function generates score, depending on which the best fit ligand is selected. KEY STAGES IN DOCKING 29

29.30. Why is docking important? • It is the key to rational drug design: The results of docking can be used to find inhibitors for specific target proteins and thus to design new drugs. • It is gaining importance as the number of proteins whose structure is known increases • In addition to new drug discovery, it is of extreme relevance in cellular biology, where function is accomplished by proteins interacting with themselves and with other molecular components 30

30.31. USES OF DOCKING Drug targetsθ Protein- ligand interactions that otherwise may be overlookedθ Better understand the Machinery of Lifeθ Enzyme-inhibitor class⟩ Antibody-antigen class⟩ Others⟩ Protein Therapiesθ Engineered Protein Enzymesθ Although the reliability of docking methods is not so high, they canθ provide new suggestions False positives rates can be reduced using several scoring functionsθ in a consensus-scoring strategy 31

31.32. APPLICATIONS Virtual screening (hit identification) Docking with a scoring function can be used to quickly screen largeθ databases of potential drugs in silico to identify molecules that are likely to bind to protein target of interest. Drug Discovery (lead optimization) Docking can be used to predict in where and in which relativeθ orientation a ligand binds to a protein (binding mode or pose). This information may in turn be used to design more potent andθ selective analogs. Bioremediation Protein ligand docking can also be used to predict pollutants that canθ be degraded by enzymes. 32

32.33. FUTURE CHALLENGES FOR DOCKING • Better Scoring Functions • High-Throughput Screening • Tractable Models of Flexibility • The so-called computational molecular docking problem is far from being solved.

There are two major bottle-necks: 1. The algorithms can handle only a limited extent of backbone flexibility 2. The availability of selective and efficient scoring functions 33

33.34. Receptor Ligand Approach Comments known known DOCK receptor based Programmes- AUTO-DOCK known unknown De novo based GROW, LEGEND unknown known Ligand based QSAR unknown unknown Combinational based Different approaches based on structural availibility 34

34.35. DE NOVO APPROACHES • De novo design is the approach to build a customized Ligand for a given receptor. • This approach involves the ligand optimization. • Ligand optimization can be done by analyzing protein active site properties that could be probable area of contact by the ligand. • The analyzed active site properties are described to negative image of protein such as hydrogen bond, hydrogen bond acceptor and hydrophobic contact region. 35

35.36. DE NOVO DRUG DESIGN De novo means start afresh, from the beginning, from¬ the scratch It is a process in which the 3D structure of receptor is used¬ to design newer molecules It involves structural determination of the lead target¬ complexes and lead modifications using molecular modeling tools. Information available about target receptor but no existing¬ leads that can interact. 36

36.37. PRINCIPLES OF DENOVO DRUG DESIGN •Assembling possible compounds and evaluating their quality.• Searching the sample space for novel structures with drug like properties. Protein Structure Build a model for Protein Structure 37

37.38. DENOVO DRUG DESIGN •In de novo design, the structure of the target should be known to a high resolution, and the binding to site must be

well defined. • This should defines not only a shape constraint but hypothetical interaction sites, typically consisting of hydrogen bonds, electrostatic and other non-covalent interactions. • These can greatly reducing the sample space, as hydrogen bonds and other anisotropic interactions can define specific orientations. 38

38.39. DERIVATION OF INTERACTION SITES A key step to model the binding site as accurately as possible. • This starts with an atomic resolution structure of the active site. • Programs like UCSF , DOCK define the volume available to a ligand by filling the active site with spheres. • Further constraints follow, using positions of H-bond acceptors and donors. • Other docking algorithms, such as FLOG, GOLD, and FlexiDock 16 use an all-atom representations to achieve fine detail. • Ray-tracing algorithms, such as SMART,represent another strategy 39

39.40. Growing Linking Lattice Based sampling Molecular dynamics based methods 40

40.41. . Fragments are added to provide suitable interactions to both key sites and space between key sites These include simple hydrocarbon chains, amines, alcohols, and even single rings. In the case of multiple seeds, growth is usually simultaneous and continues until all pieces have been integrated into a single molecule. A Single Key Building Block is the starting point or Seed 41

41.42. GROWING 42

42.43. Linking 43

43.44. LINKING 44

44.45. LINKING The fragments, atoms, or building blocks are either′ placed at key interaction sites. They are joined together using pre-defined rules

to′yield a complete molecule. Linking groups or linkers may be predefined or generated to satisfy all required conditions . 45

45.46. Lattice based method The lattice is placed in the binding site, and atoms around key interaction sites are joined using the shortest path. Then various iterations, each of which includes translation, rotation or mutation of atoms, are guided by a potential energy function, eventually leading to a target molecule. 46

46.47. 47

47.48. Molecular Dynamics Methods The building blocks are initially randomly placed and then by MD simulations allowed to rearrange. After each rearrangement certain bonds were broken and the process repeated. During this procedure high scoring structures were stored for later evaluation. 48

48.49. SCORING • Each solution should be tested to decide which is the most promising. This is called as scoring. • Programs such as LEGEND18, LUDI19, Leap-Frog16, SPROUT20, HOOK21, and PRO-LIGAND22 attempt this using different scoring techniques • These scoring functions vary from simple strict constraints and H-bond placement to explicit force fields and empirical or knowledge- based scoring methods. 49

49.50. • Programs like GRID and LigBuilder3 set up a grid in the binding site and then assess interaction energies by placing probe atoms or fragments at each grid point. • Scoring functions guide the growth and optimization of structures by assigning fitness values to the sampled space Scoring functions attempt to approximate the binding free energy by substituting the exact physical model with simplified statistical methods. • SCORING-(CONT..) 50

50.51. • Empirical scoring functions are a weighted sum of individual ligand–receptor interactions. • Apart from scoring functions, attempts have been

made to use NMR, X-ray analysis and MS to validate the fragments Force fields usually involve more computation than the other types of scoring functions eg:- LEGEND SCORING-(CONT..) 51

51.52. METHOD PROGRAMS AVAILABLE Site point connection method LUDI Fragment connection method SPLICE, NEW LEAD, PRO-LIGAND Sequential build up methods LEGEND, GROW, SPORUT Random connection and disconnection methods CONCEPTS, CONCERTS, MCDNLG 52

52.53. DE NOVA DESIGN OF INHIBITOR FOR HIV-I PROTEASE INHIBITOR An impressive example of the application of SBDD was the design of the HIV-I protease Inhibitor. The starting point is the series of X-ray structures of the enzyme and′ enzyme-inhibitor complex. The enzyme is made up of two equal halves. HIV protease is a symmetrical molecule with 2 equal halves and an′ active site near its center like butterfly. 53

53.54. DE NOVA DESIGN OF INHIBITOR FOR HIV-I PROTEASE INHIBITOR For most such symmetrical molecules′ with two equal halves and an active site near its center like butterfly For most such symmetrical′molecules,both halves have a “business area”,or active site,that carries out the enzymes job. But HIV protease has only one such′ active site in the center of the molecule where the two halves meet. 54

54.55. HIV 1 PROTEASE INHIBITOR Structure of enzyme Enzyme with inhibitor 55

55.56. 56

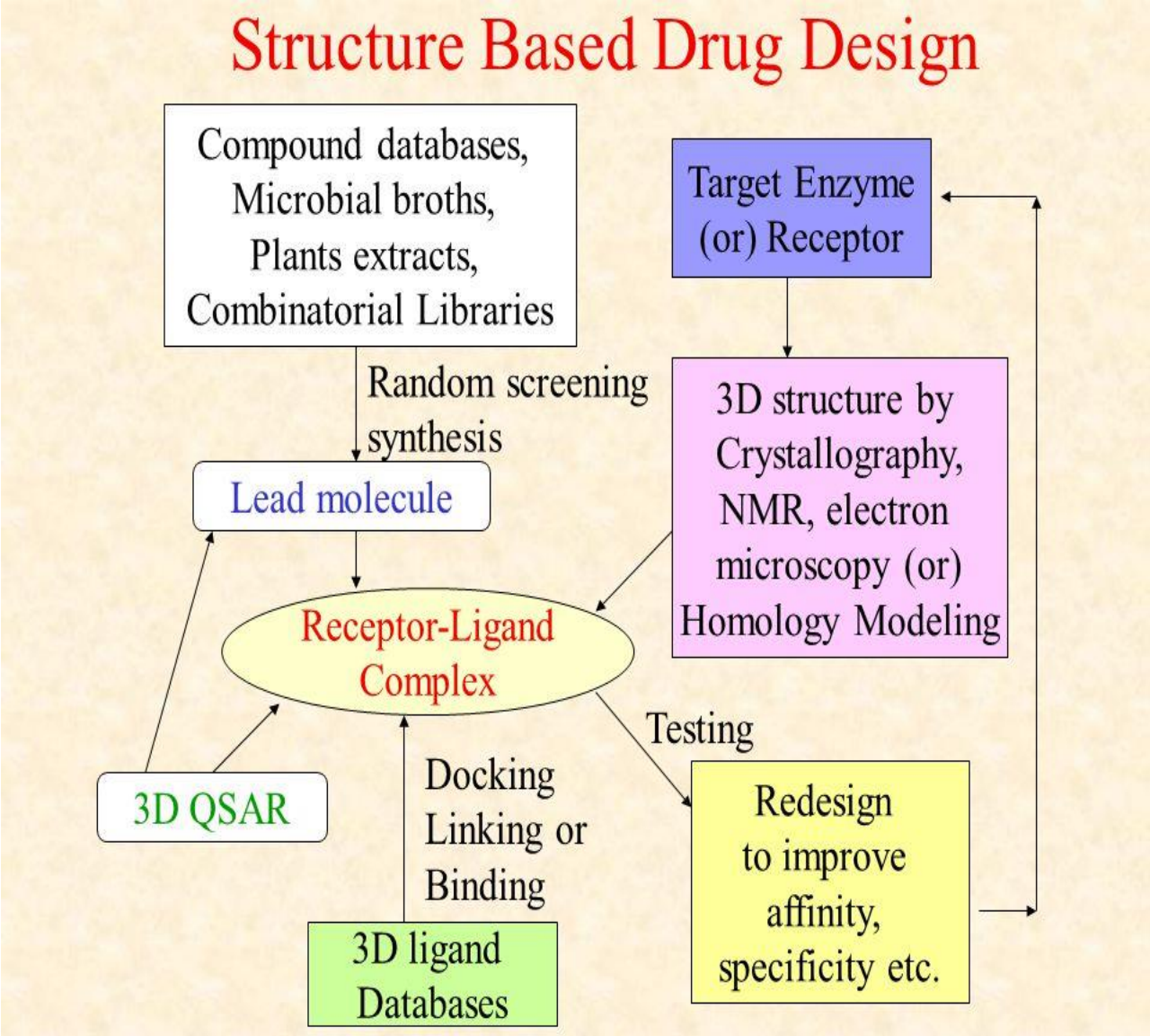
56.57. 57

57.58. EXAMPLES OF DRUGS DESIGNED BY STRUCTURE- BASED METHODS INHIBITOR TARGET DISEASE HUMAN RENIN ANTI

HYPERTENSION COLLAGENASE AND STROMELYSIN ANTICANCER ,ANTIARTHRITIS PURINE NUCLEOTIDE PHOSPHORYLASE ANTIDEPRESSANT THYMIDYLATE SYNTHASE ANTIPROLIFERATION 58

58.59. Although a relatively new design method, de novo design′ will play an ever-increasing role in modern drug design. Though yet not able to automatically generate viable drugs by itself, it is able to give rise to novel and often unexpected drugs when coupled with HTS, is proving to reduce drug′ design turn around time. 59

59.60. IMPROVE QUALITY OF LIFE The emphasis now is not just on finding new ways to treat′ human disease, but also on improving the quality of life of people.



DRUG DISCOVERY CYCLE

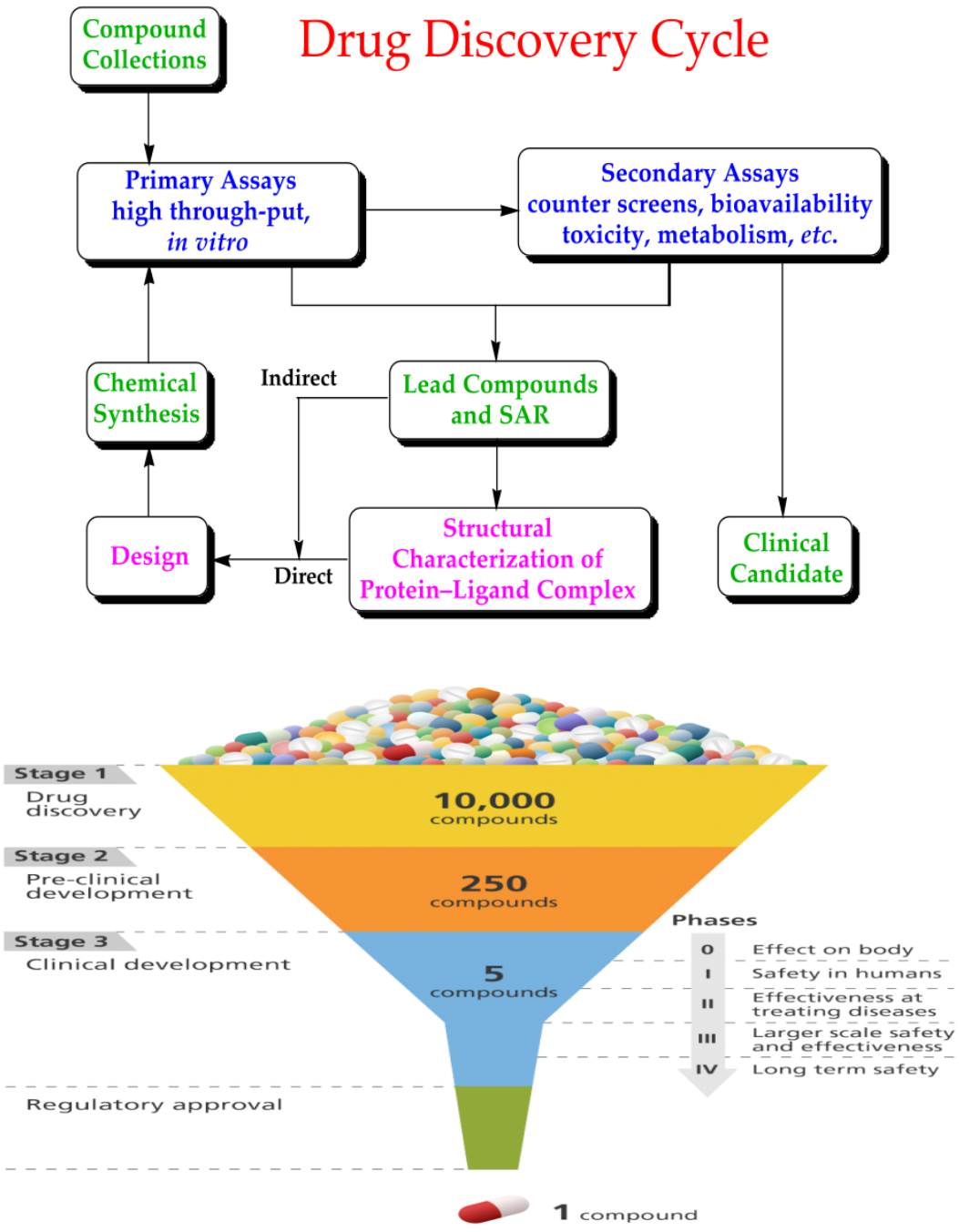


Fig.2.7:Drug statistics & Discovery cycle

Chapter 3

Graphical User Interface (GUI)

- Introduction
- Graphical user interface (GUI)
- GUI overview
- How does a GUI work?
- Benefits of GUI
- Some examples of a GUI operating system
- Are all operating systems GUI?
- What are examples of a GUI interface?
- How does the user interact with a GUI?
- Computer operating systems information
- Summary

3.1 Introduction:

A graphical user interface (GUI) presents a user-friendly mechanism for interacting with an application. Short for Graphical User Interface, a GUI (pronounced as either G-U-I or gooey) allows the use of icons or

other visual indicators to interact with electronic devices, rather than using only text via the command line. These are sometimes called controls or widgets—short for

window gadgets. A GUI component is an object with which the user interacts via the mouse, the keyboard or another form of input, such as voice recognition. Java's so-called Swing GUI components from the javax .swing package 2[1]

A window is a (usually) rectangular portion of the monitor screen that can display its contents (e.g., a program, icons, a text file or an image) seemingly independently of the rest of the display screen. A major feature is the ability for multiple windows to be open simultaneously. Each window can display a different application, or each can display different files (e.g., text, image or spreadsheet files) that have been opened or created with a single application. [2]

An icon is a small picture or symbol in a GUI that represents a program (or command), a file, a directory or a device (such as a hard disk or floppy). Icons are used both on the desktop and within application programs. Examples include small rectangles (to represent files), file folders (to represent directories), a trash can (to indicate a place to

dispose of unwanted files and directories) and buttons on web browsers (for navigating to previous pages, for reloading the current page, etc.)[5].

3.2 Graphical user interface (GUI)

Graphical User interfaces rely much more heavily on the mouse. A typical example of this type of interface is any version of the Windows Operating System.

The main advantages are:

1. Less expert knowledge is required to use it (more user friendly)

2. Easier to navigate can look through folders quickly in a guess and check manner.

The main disadvantages are:

1. Typically decreased options (less powerful)

2. Typically less customizable.Not easy to use one button for tons of different variations.¬Graphical User Interfaces are more common than text-based interfaces in modern computing[5].

3.3GUI overview

Below is a picture of the Windows 7 Desktop and an example of a GUI.

Fig 3.1: GUI overview [].

3.4 How does a GUI work?

A GUI uses windows, icons, and menus to carry out commands, such as opening, deleting, and moving files. Although many GUI operating systems are navigated through the use of a mouse, the keyboard can also be utilized by using keyboard shortcuts or arrow keys [5].

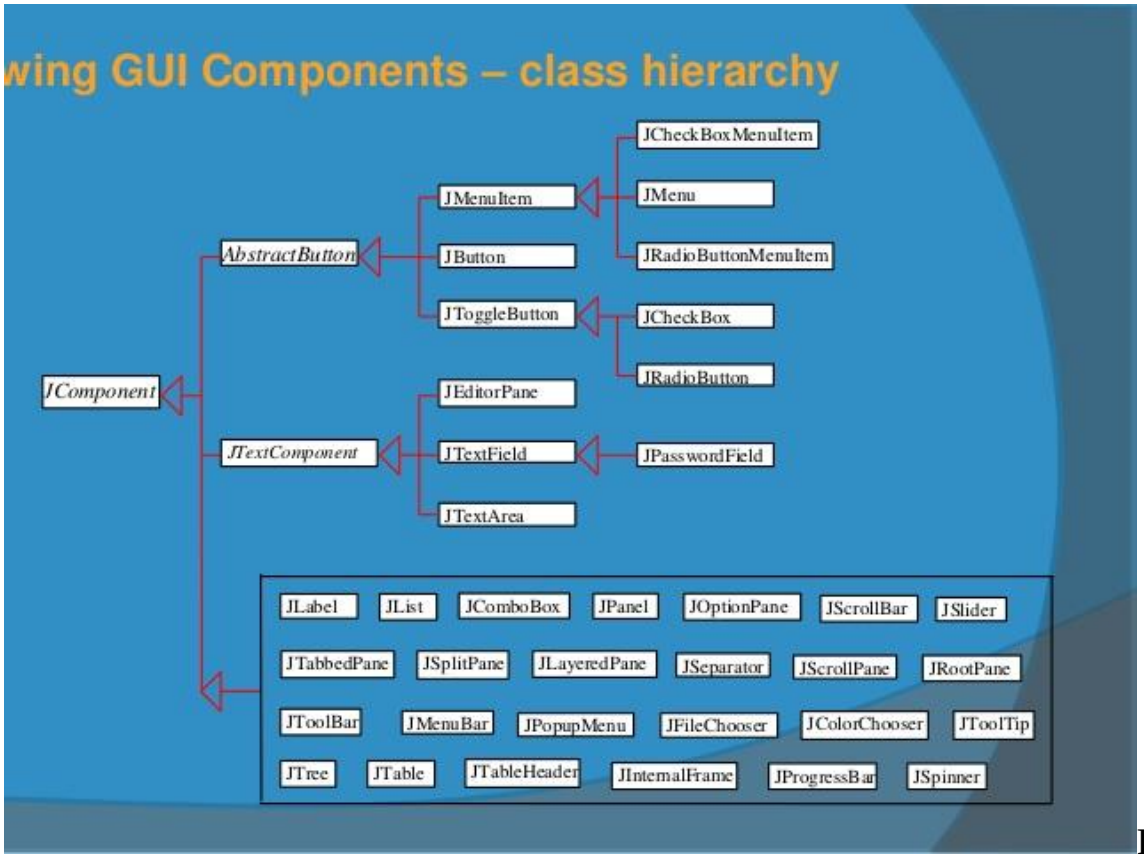


Fig:

Fig 3.5: An example of a GUI work hierarchy[1].

Frame

In graphics and desktop publishing applications, a rectangular area in which text or graphics can appear is termed as a frame. Frames are rectangular areas meant

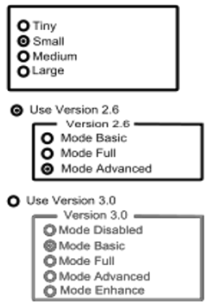


Fig.3.5.1: Frame [1]

Inserting graphics and text. They allow users to place objects wherever they want to on the page [1].

Window

Window is the total visible screen of any application. It consists of a visual area that contains some of the graphical user interface of the program. A window is framed by a window decoration. It has a

Fig 3.5.2: **Window**

rectangular shape that can overlap with the area of other windows. It displays the output and allows input to one or more processes[1].

Label

A label is a graphical control element, which displays text on a form. It is a static control; having no interactivity. A label is generally used to identify a nearby text box[3].

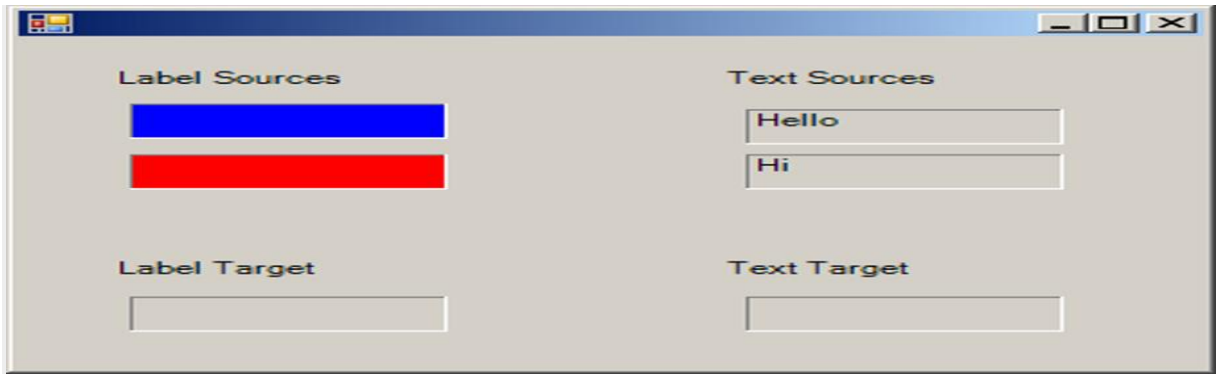


Fig 3.5.3: Label

A label in GUI is just like a piece of paper, polymer, cloth, metal, or other material on a container or product, written or printed information about the product. In computing, labels are used when the texts are written for informational and naming purpose[3].

Text Box

A text box is a graphical control element often appears with a label and is intended to enable the user to input text information used by the program. It is an area where user can input data and information.

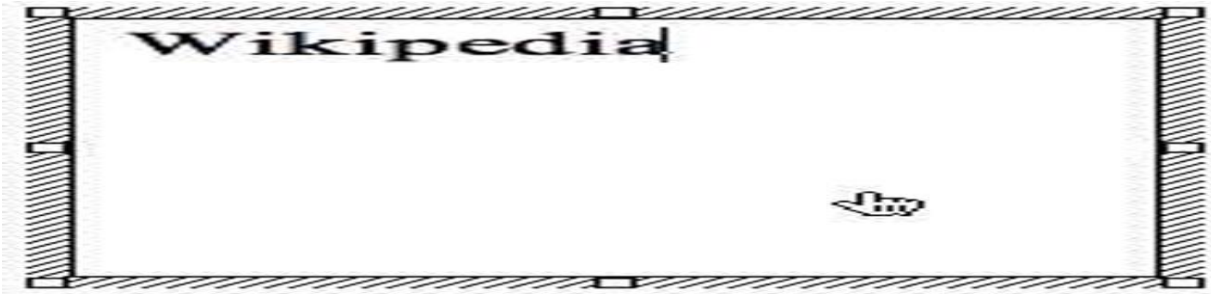


Fig 3.5.4: Text Box .

Text field

A text field is a text control GUI element that enables the user to type a small amount of text. When the user indicates that text entry is complete, the text field processes an event [3].

Fig3.5.5: Text field

Menu

Menu is a control that allows the user to select an option out of a list of options.

It is a list of options or commands presented to an operator by a computer[1].

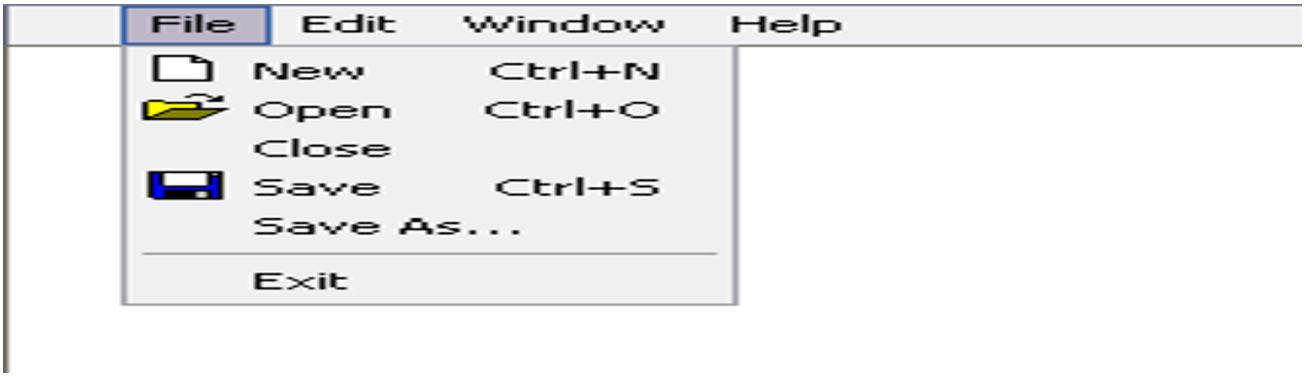


Fig 3.5.6: Menu [Buttons]

Buttons are control which can be clicked upon to select an option from a selection of options. Its name comes from the mechanical push-button group on a car radio receiver[2].

Fig 3.5.7: Buttons

Combo Box

Combo box is a combination of a single-line text box and a drop-down list or list box. It allows the user to either type a value directly into the control or choose from the list of existing options. It is very useful when a user has to select a certain option among various options [3].

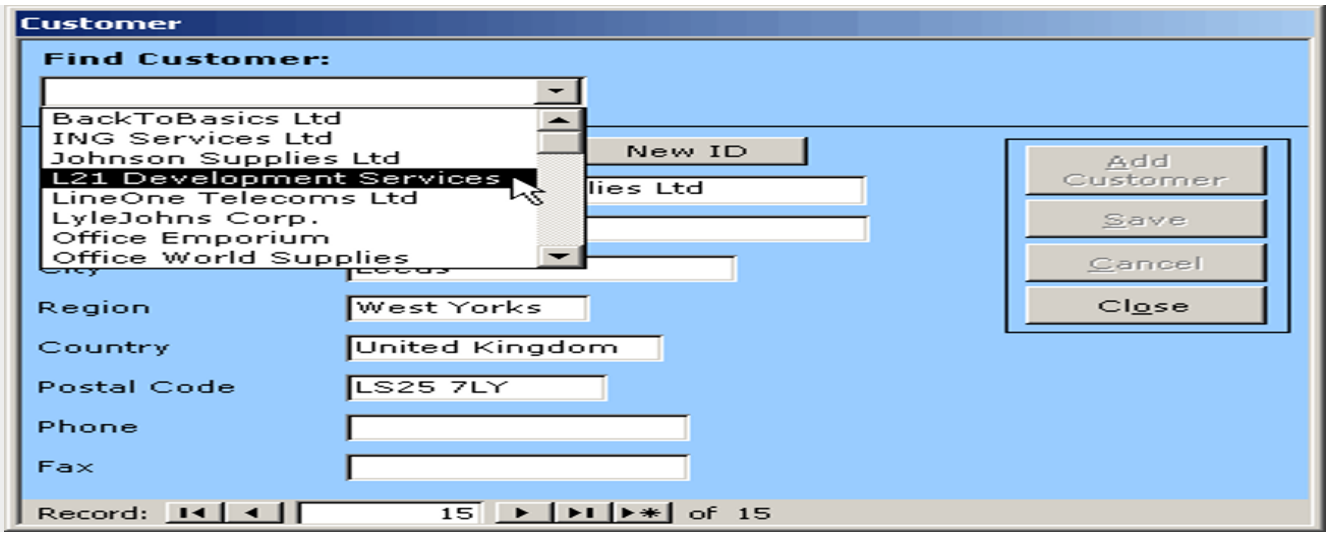


Fig 3.5.8: Combo Box

Radio Button

Radio buttons always appear in pairs or larger groups, and only one option in the group can be selected at a time. Selecting a new item from the group's buttons also de-selects the previously selected button. Radio buttons were named after the physical buttons used on older radios to select Presentations .

Fig 3.5.8: Radio Button

When one of the buttons was pressed, other buttons would pop out, leaving the pressed button the only button in the "pushed in" position [5].

Check Box

Check box is a graphical element that allows user to make selection among the given alternatives. Check box are often presented as a small box in the shape of square. A simple click on the check box marks the box and makes a visible selection in the computer. A check box is usually accompanied by a label to provide information to the user about the choices to be made [5].

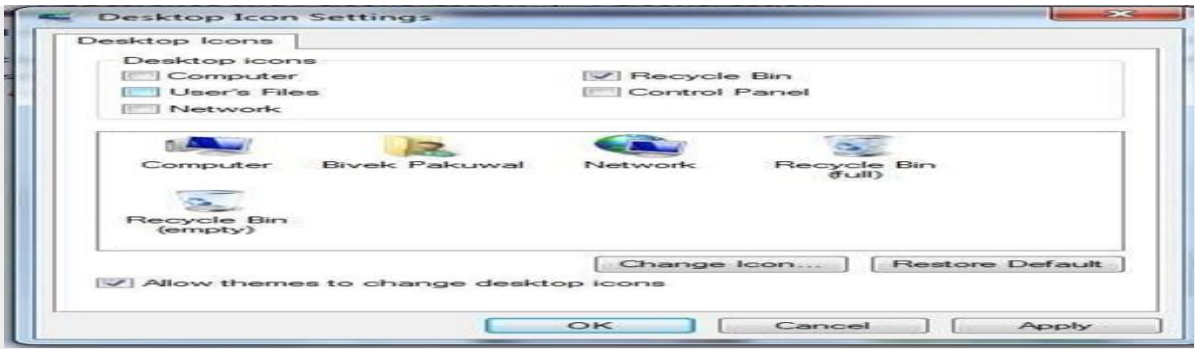


Fig 3.5.9: Check Box

Tree view

A tree view is a graphical control element that presents a hierarchical view of information. Each item (often called a branch or a node) can have a number of sub- items. This is often visualized by indentation in a list. An item can be expanded to reveal sub-items, if any exist, and collapsed to hide sub-items. Tree

views can be seen in file manager applications, where they allow the user to navigate the file system directories [2].

Fig 3.5.10: Tree view

Tab

Tab is a graphical control element. A tab allows multiple documents or panels to be contained within a single window. It is an interface style most commonly associated with web browsers, web applications and text editors. Tabs are popular in use as a navigational widget for switching between sets of documents [4].

Fig3.5.11: Tab

3.5 Benefits of GUI

A major advantage of GUIs is that they make computer operation more intuitive, and thus easier to learn and use. For example, it is much easier for a new user to move a file from one directory to another by dragging its icon with the mouse than by having to remember and type seemingly arcane commands to accomplish the same task [5].

Adding to this intuitiveness of operation is the fact that GUIs generally provide users with immediate, visual feedback about the effect of each action. For example, when a user deletes an icon representing a file, the icon immediately disappears, confirming that the file has been deleted (or at least sent to the trash can). This contrast with the situation for a CLI, in which the user types a delete command (inclusive of the name of the file to be deleted) but receives no automatic feedback indicating that the file has actually been removed [3].

In addition, GUIs allow users to take full advantage of the powerful multitasking (the ability for multiple programs and/or multiple instances of single programs to run simultaneously) capabilities of modern operating systems by allowing such multiple programs and/or instances to be displayed simultaneously. The result is a large increase in the flexibility of computer use and a consequent rise in user productivity [4].

But the GUI has become much more than a mere convenience. It has also become the standard in human-computer interaction, and it has influenced the work of a

generation of computer users . Moreover, it has led to the development of new types of applications and entire new industries. An example is desktop publishing, which has revolutionized (and partly wiped out) the traditional printing and typesetting industry [2].

Examples of a GUI operating system

1. GNOME.
2. KDE.
3. Any Microsoft program (i.e. Word, Excel, Outlook).
4. Internet browser (i.e. Internet Explorer, Chrome, Firefox)[3]

Other operating systems GUI

No. Early command line operating systems like MS-DOS and even some versions of Linux today have no GUI interface [3].

Other examples of a GUI interface

1. GNOME
2. KDE
3. Any Microsoft program (i.e. Word, Excel, Outlook)
4. Internet browser (i.e. Internet Explorer, Chrome, Firefox)[3]

3.6 How does the user interact with a GUI?

Typically the user uses a pointing device such as the mouse to interact and use most aspects of the GUI. However, it is also possible to interact with a GUI using a keyboard or other input device[3].

3.7 Summary

GUI helps to make the program interactive to the user so that one can use various tools provided in the Mat lab GUI interface to get the desired layout area.

Chapter 4

SQL (Structured Query Language)

- Introduction
- SQL standard and proprietary extensions
- SQL Language elements
- SELECT statements
- SQL data control
- Definition and manipulation
- SQL data manipulation
- SQL commands and syntax
- SQL-on- Hardoop tools
- SQL data definition
- SQL data control
- Example SQL learning more about SQL
- Overview

4.1 Introduction

SQL History SQL standard and proprietary extensions SQL Language elements SELECT statements SQL data control, definition and manipulation SQL data manipulation SQL commands and syntax SQL-on-Hadoop tools SQL data definition SQL data control Examples Learning more about SQL Overview Reference

4.2 SQL

SQL (Structured Query Language) is a standardized programming language used for managing relational databases and performing various operations on the data in them. Initially created in the 1970s, SQL is regularly used by database administrators, as well as by developers writing data integration scripts and data analysts looking to set up and run analytical queries[].

The uses of SQL include modifying database table and index structures; adding, updating and deleting rows of data; and retrieving subsets of information from within a database for transaction processing and analytics applications. Queries and other SQL operations take the form of commands written as statements -- commonly used SQL statements include select, add, insert, update, delete, create, alter and truncate[].

SQL became the de facto standard programming language for relational databases after they emerged in the late 1970s and early 1980s. Also known as SQL databases, relational systems comprise a set of tables containing data in rows and columns. Each column in a table corresponds to a category of data -- for example, customer name or address -- while each row contains a data value for the intersecting column [1].

4.3 SQL History

The origins of the SQL take us back to the 1970s, when in the IBM laboratories, new database software was created - System R. And to manage the data stored in System R, the SQL language was created. At first it was called SEQUEL, a name which is still used as an alternative pronunciation for SQL, but was later renamed to just SQL.

In 1979, a company called Relational Software, which later became Oracle, saw the commercial potential of SQL and released its own modified version, named Oracle V2.

Now into its third decade of existence, SQL offers great flexibility to users by supporting distributed databases, i.e. databases that can be run on several computer networks at a time. Certified by ANSI and ISO, SQL has become a database query language standard, lying in the basis of a variety of well established database applications on the Internet today. It serves both industry-level and academic needs and is used on both individual computers and corporate servers. With the progress in database technology SQL-based applications have become increasingly affordable for the regular user. This is due to the introduction of various open-source SQL database solutions such as My SQL, Postage SQL light, Firebird, and many more [2].

4.5 SQL standard and proprietary extensions

An official SQL standard was adopted by the American National Standards Institute (ANSI) in 1986 and then by the International Organization for Standardization, known as ISO, in 1987. More than a half-dozen joint updates to the standard have been released by the two standards development bodies since then; as of this writing, the most recent version is SQL:2011, approved that year[].

Both proprietary and open source relational database management systems built around SQL are available for use by organizations. They include Microsoft SQL Server, Oracle Database, IBM DB2, SAP HANA, SAP Adaptive Server, My SQL (now owned by Oracle) and Postgre SQL. However, many of these database products support SQL with proprietary extensions to the standard language for proceduralprogramming and other functions. For example, Microsoft offers a set of

extensions called Transact-SQL (T-SQL), while Oracle's extended version of the standard is PL/SQL. As a result, the different variants of SQL offered by vendors aren't fully compatible with one another[1].

4.6 SQL Language elements

The SQL language is based on several elements. For the convenience of SQL developers all necessary language commands in the corresponding database management systems are usually executed through a specific SQL command-line interface (CLI).

- **Clauses** - the clauses are components of the statements and the queries
- **Expressions** - the expressions can produce scalar values or tables, which consist of columns and rows of data
- **Predicates** - they specify conditions, which are used to limit the effects of the statements and the queries, or to change the program flow
- **Queries** - a query will retrieve data, based on a given criteria
- **Statements** - with the statements one can control transactions, program flow, connections, sessions, or diagnostics. In database systems the SQL statements are used for sending queries from a client program to a server where the databases are stored. In response, the server processes the SQL statements and returns replies to the client program. This allows users to execute a wide range of amazingly fast data manipulation operations from simple data inputs to complicated queries.

4.7 SELECT statements

An SQL SELECT statement retrieves records from a database table according to clauses (e.g., FROM and WHERE) that specify criteria. The syntax is:

```
SELECT column1, column2 FROM table1, table2 WHERE column2='value';
```

In the above SQL statement:

- The SELECT clause specifies one or more columns to be retrieved; to specify multiple columns, use a comma and a space between column names. To retrieve all columns, use the wild card * (an asterisk).
- The FROM clause specifies one or more tables to be queried. Use a comma and space between table names when specifying multiple tables.
- The WHERE clause selects only the rows in which the specified column contains the specified value. The value is enclosed in single quotes (e.g., WHERE last_name='Vader').
- The semicolon (;) is the statement terminator. Technically, if you're sending only one statement to the back end, you don't need the statement terminator; if you're sending more than one, you need it. It's best practice to include it.

Note: SQL is not case sensitive (i.e., SELECT is the same as select). For readability purposes, some programmers use uppercase for commands and clauses, and lowercase for everything else [3].

4.8 SQL data control, definition and manipulation

SQL is a language designed to store data, but the data stored in an SQL database is not static. It can be modified at any time with the use of several very simple commands. The SQL syntax is pretty much self explanatory, which makes it much easier to read and understand.

4.9 SQL data manipulation

Data manipulation is essential for SQL tables - it allows you to modify an already created table with new information, update the already existing values or delete them.

With the INSERT statement, you can add new rows to an already existing table. New rows can contain information from the start, or can be with a NULL value. [2]

4.10 SQL commands and syntax

SQL commands are divided into several different types, among them data manipulation language (DML) and data definition language (DDL) statements, transaction controls and security measures. The DML vocabulary is used to

retrieve and manipulate data, while DDL statements are for defining and modifying database structures. The transaction controls help manage transaction processing, ensuring that transactions are either completed or rolled back if errors or problems occur. The security statements are used to control database access as well as to create user roles and permissions.

SQL syntax is the coding format used in writing statements. Figure 1 shows an example of a DDL statement written in Microsoft's T-SQL to modify a database table in SQL Server 2016[]:

```
Use tempdb
GO

CREATE TABLE Sample (Numbers INT ) ;
GO

INSERT INTO Sample(Numbers) VALUES (10)
GO 20

ALTER TABLE Sample
   ALTER COLUMN Numbers DECIMAL (4, 2) WITH (ONLINE = ON);
GO

SP_HELP Sample
GO

DROP TABLE Sample
GO
```

4.11 SQL-on-Hadoop tools

SQL-on-Hadoop query engines are a newer offshoot of SQL that enable organizations with big data architectures built around Hadoop systems to take advantage of it instead of having to use more complex and less familiar languages -- in particular, the Map Reduce programming environment for developing batch processing applications[].

More than a dozen SQL-on-Hadoop tools have become available through Hadoop distribution providers and other vendors; many of them are open source software or commercial versions of such technologies. In addition, the Apache Spark processing engine, which is often used in conjunction with Hadoop, includes a Spark SQL module that similarly supports SQL-based programming.

In general, SQL-on-Hadoop is still an emerging technology, and most of the available tools don't support all of the functionality offered in relational implementations of SQL. But they're becoming a regular component of Hadoop deployments as companies look to get developers and data analysts with SQL skills involved in programming big data applications [1].

4.12 SQL data definition

Data definition allows the user to define new tables and elements.

- **CREATE** - with the CREATE statement you can create a new table in an existing database.

  An example of an SQL CREATE

- CREATE TABLE phonebook(phone VARCHAR(32), firstname VARCHAR(32), lastname VARCHAR(32), address VARCHAR(64));
-
- **DROP** - with the DROP statement in SQL you can delete tables, which you no longer need

  An example of an SQL DROP

  DROP TABLE phonebook;

- **TRUNCATE** - with the TRUNCATE statement, you can delete all the content in the table, but keep the actual table intact and ready for further use

  An example of an SQL TRUNCATE

TRUNCATE TABLE phonebook;

- The **ALTER** statement permits the user to modify an existing object in various ways -- for example, by adding a column to an existing table.

  ALTER TABLE phonebook RENAME TO contacts

4.13 SQL data control

SQL allows the user to define the access each of the table users can have to the actual table.

- **GRANT** - with the GRANT statement, you can authorize users to modify the selected table

  An example of an SQL GRANT

  ```
  GRANT ALL PRIVILEGES ON database_name TO database_user;
  ```

- **REVOKE** - with the REVOKE statement you can remove all privileges, previously granted to a user.

  An example of an SQL REVOKE

  ```
  REVOKE ALL PRIVILEGES ON database_name TO database_user ;  [2]
  ```

Examples

Following are examples of SQL SELECT statements:

- To select all columns from a table (Customers) for rows where the Last_Name column has Smith for its value, you would send this SELECT statement to the server back end:

```
SELECT * FROM Customers WHERE Last_Name='Smith';
```

The server back end would reply with a result set similar to this:

```
+---------+-----------+------------+
| Cust_No | Last_Name | First_Name |
+---------+-----------+------------+
| 1001    | Smith     | John       |
| 2039    | Smith     | David      |
| 2098    | Smith     | Matthew    |
+---------+-----------+------------+
3 rows in set (0.05 sec)
```

- To return only the Cust_No and First_Name columns, based on the same criteria as above, use this statement:

```
SELECT Cust_No, First_Name FROM Customers WHERE Last_Name='Smith';
```

The subsequent result set might look like:

```
+---------+------------+
| Cust_No | First_Name |
+---------+------------+
```

```
| 1001    | John       |
| 2039    | David      |
| 2098    | Matthew    |
+---------+------------+
3 rows in set (0.05 sec)
```

To make a WHERE clause find inexact matches, add the pattern-matching operator LIKE. The LIKE operator uses the % (percent symbol) wild card to match zero or more characters, and the underscore (_) wild card to match exactly one character. For example:

- To select the First_Name and Nickname columns from the Friends table for rows in which the Nicknamecolumn contains the string "brain", use this statement:

```
SELECT First_Name, Nickname FROM Friends WHERE Nickname LIKE '%brain%';
```

The subsequent result set might look like:

```
+------------+------------+
| First_Name | Nickname   |
+------------+------------+
| Ben        | Brainiac   |
| Glen       | Peabrain   |
```

```
| Steven     | Nobrainer  |

+------------+------------+

3 rows in set (0.03 sec)
```

- To query the same table, retrieving all columns for rows in which the First_Name column's value begins with any letter and ends with "en", use this statement:

```
SELECT * FROM Friends WHERE First_Name LIKE '_en';
```

The result set might look like:

```
+------------+------------+-----------+

| First_Name | Last_Name  | Nickname  |                    +------------+-----
-------+-----------+

| Ben        | Smith      | Brainiac  |

| Jen        | Peters     | Sweetpea  |+------------+------------+-----------+

2 rows in set (0.03 sec)
```

- If you used the % wild card instead (e.g., '%en') in the example above, the result set might look like:

```
+------------+------------+-----------+
| First_Name | Last_Name  | Nickname  |
+------------+------------+-----------+
| Ben        | Smith      | Brainiac  |
| Glen       | Jones      | Peabrain  |
| Jen        | Peters     | Sweetpea  |
| Steven     | Griffin    | Nobrainer |
```

- +------------+------------+-----------+

4 rows in set (0.05 sec)

Learning more about SQL

To learn more about SQL programming, Indiana University students, faculty, and staff can download materials for self-study from IT Training.

For the general public, various online tutorials are available, such as the w3schools.com SQL Tutorial[].

4.13 Overview

Structured Query Language (SQL) is a specialized language for updating, deleting, and requesting information from databases. SQL is anANSI and ISO standard, and is the de facto standard database query language. A variety of established database products support SQL, including products from Oracle and Microsoft SQL Server. It is widely used in both industry and academia, often for enormous, complex databases.

In a distributed database system, a program often referred to as the database's "back end" runs constantly on a server, interpreting data files on the server as a standard relational database. Programs on client computers allow users to manipulate that data, using tables, columns, rows, and fields. To do this, client programs send SQL statements to the server.

4.15 Conclusion

There are some people who worked on Drug Designing. If we can be able to design a digital prescription by annual survey. There will be no Quack doctors. We can get rid of many diseases. We use Graphic User Interface, Server Query Language for implementing the software. There will be only authorized doctor who can be able to access the software. Only registered doctor will be able to access the software by their registered number.

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